```
$

FILE 'HOME' ENTERED AT 10:30:45 ON 01 JUN 2002

=> file medline caplus biosis embase scisearch agricola
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'MEDLINE' ENTERED AT 10:31:15 ON 01 JUN 2002

FILE 'CAPLUS' ENTERED AT 10:31:15 ON 01 JUN 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'BIOSIS' ENTERED AT 10:31:15 ON 01 JUN 2002
COPYRIGHT (C) 2002 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'EMBASE' ENTERED AT 10:31:15 ON 01 JUN 2002
COPYRIGHT (C) 2002 Elsevier Science B.V.  All rights reserved.

FILE 'SCISEARCH' ENTERED AT 10:31:15 ON 01 JUN 2002
COPYRIGHT (C) 2002 Institute for Scientific Information (ISI) (R)

FILE 'AGRICOLA' ENTERED AT 10:31:15 ON 01 JUN 2002

=> s (dna methylation) (p) inhibit?
L1        3344 (DNA METHYLATION) (P) INHIBIT?

=> s cytidine or decitabine
L2       31295 CYTIDINE OR DECITABINE

=> s l1 (p) l2
L3         100 L1 (P) L2

=> s (histone deacetylase) (p) inhibit?
L4        3881 (HISTONE DEACETYLASE) (P) INHIBIT?

=> s (hydroxamic acid) or trichostatin or oxamflatin or (bishydroxamic acid) or pyroxamide
L5       15569 (HYDROXAMIC ACID) OR TRICHOSTATIN OR OXAMFLATIN OR (BISHYDROXAMI
               C ACID) OR PYROXAMIDE

=> s l4 (p) l5
L6        1986 L4 (P) L5

=> s l3 (p) l5
L7           2 L3 (P) L5

=> duplicate remove l7
DUPLICATE PREFERENCE IS 'BIOSIS, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L7
L8           2 DUPLICATE REMOVE L7 (0 DUPLICATES REMOVED)

=> d l8 1-2 ibib abs

L8   ANSWER 1 OF 2  BIOSIS  COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER:   2002:129878  BIOSIS
DOCUMENT NUMBER:    PREV200200129878
TITLE:              Reactivation of a silenced, methylated p16INK4a gene by
                    low-dose 5-aza-2'-deoxycytidine requires activation of the
                    p38 map kinase signal transduction pathway.
AUTHOR(S):          Lavelle, Donald (1); DeSimone, Joseph; Hankewych, Maria;
                    Kousnetzova, Tatiana; Chen, Yi-Hsiang
CORPORATE SOURCE:   (1) Department of Medicine, University of Illinois at
                    Chicago, Chicago, IL USA
SOURCE:             Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp.
                    105a. http://www.bloodjournal.org/. print.
                    Meeting Info.: 43rd Annual Meeting of the American Society
                    of Hematology, Part 1 Orlando, Florida, USA December 07-11,
                    2001
```

ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB ***DNA*** ***methylation*** silences the expression of multiple tumor supressor genes in many types of tumors by inducing repressive chromatin structures mediated by binding of methylated DNA binding (MBD) proteins associated with protein complexes containing histone deacetylase (HDAC) activity and chromatin remodeling factors. Treatment with the DNA demethylating drug 5-aza-2'-deoxycytidine (***decitabine*** ; DAC) reactivates the expression of silenced, methylated tumor suppressor genes by alleviating methylation-mediated repression. The synergistic reactivation of silenced, methylated genes by a combination of the HDAC ***inhibitor*** ***trichostatin*** A with low doses of DAC inducing limited demethylation demonstrated the important role of HDAC in the maintenance of methylation-mediated gene silencing (Cameron et al, Nat Genet 21:103, 1999). Whether DAC induces other activities that may be essential in the reactivation of silenced, methylated genes has not been investigated. Environmental and pharmacologic stress activates alternative map kinase signal tranduction pathways resulting in MSK 1-mediated phosphorylation of a minute fraction of histone H3 on serine 10. Phosphorylation of H3 increases sensitivity to hyperacetylation by HDAC ***inhibitors*** and histone acetyltransferases. Our objective in these experiments was to: 1) determine whether DAC treatment activated map kinase signal transduction pathways, and 2) investigate the role of map kinase pathways in the reactivation of silenced, methylated tumor suppressor genes. We observed that DAC treatment reactivated expression of a silenced, methylated p16INK4a gene in HS-Sultan cells in a dose-dependent manner (10-7 to 10-6 M). Phosphorylation of p38 map kinase was increased in a linear, dose-dependent manner at DAC concentrations ranging from 10-8 to 10-6 M. No activation of ERK 1/2 was observed. Increased phosphorylation of p38 was observed as early as 12 hours following drug addition. The ability of DAC to reactivate p16INK4a expression was ***inhibited*** by the p38 map kinase ***inhibitor*** SB203580 (10muM) at low doses (10-7 M) but not high doses (10-6 M) of DAC. The degree of ***inhibition*** was reduced with increasing DAC dose. The ERK 1/2 ***inhibitor*** PD098059 had no effect. Neither SB203580 or PD098059 affected cell growth and therefore the ***inhibition*** of p16INK4a reactivation was not due to ***inhibition*** of DAC incorporation into DNA H89 (10muM), at a concentration shown to preferentially ***inhibit*** MSK 1 (Thomson et al, EMBO J:4779, 1999), also ***inhibited*** reactivation of p16INK4a at low doses of DAC, suggesting that MSK 1-mediated histone H3 phosphorylation was required for p16INK4a reactivation. Our results demonstrate that activation of the p38 map kinase signal transduction pathway is required for reactivation of a silenced methylated p16INK4 gene by low dose DAC and suggest that this is due to the induction of an active chromatin configuration through phosphorylation of histone H3 by MSK 1. Therefore, reactivation of a silenced, methylated p16INK4a tumor suppressor gene at low doses of DAC requires both a reduction of ***DNA*** ***methylation*** density leading to loss of repressive MBDHDAC complexes and induction of an active chromatin configuration through the p38 map kinase signal transduction pathway.

L8 ANSWER 2 OF 2 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 1998:617103 SCISEARCH
THE GENUINE ARTICLE: 108BR
TITLE: Trichostatin A causes selective loss of DNA methylation in Neurospora
AUTHOR: Selker E U (Reprint)
CORPORATE SOURCE: UNIV OREGON, INST MOL BIOL, EUGENE, OR 97403 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (4 AUG 1998) Vol. 95, No. 16, pp. 9430-9435.
Publisher: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418.
ISSN: 0027-8424.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 69
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

```
AB      Both   ***DNA***     ***methylation***   and hypoacetylation of core
     histones are frequently associated with repression of gene expression.
     Possible connections between these processes mere investigated by taking
     advantage of genes controlled by methylation in Neurospora crassa.
       ***Trichostatin***   A (TSA), a potent   ***inhibitor***   of histone
     deacetylase, derepressed a copy of hph that was repressed by   ***DNA***
       ***methylation***   which resulted from repeat-induced point mutation
     (RIP) acting on sequences flanking hph. Derepression by TSA was comparable
     to derepression by the   ***inhibitor***   of   ***DNA***
       ***methylation***   , 5-aza-  ***cytidine***   . TSA treatment also
     repressed an allele of am whose expression depends on methylation of an
     adjacent transposon, Tad.   ***DNA***     ***methylation***   in the hph
     and Tad/am regions was greatly reduced by TSA treatment. TSA also caused
     hypomethylation of other methylated alleles of ant generated by RIP. Hn
     contrast, TSA did not affect methylation of several other methylated
     genomic sequences examined, including the nucleolar rDNA and the
     inactivated transposon Punt(RIP1). Several possible models are discussed
     for the observed selective demethylation induced by TSA. The implication
     that acetylation of chromatin proteins can directly or indirectly control
       ***DNA***     ***methylation***   raises the possibility that connections
     between protein acetylation and   ***DNA***     ***methylation***   result
     in self-reinforcing epigenetic states.


=> d his

     (FILE 'HOME' ENTERED AT 10:30:45 ON 01 JUN 2002)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     10:31:15 ON 01 JUN 2002
L1          3344 S (DNA METHYLATION) (P) INHIBIT?
L2         31295 S CYTIDINE OR DECITABINE
L3           100 S L1 (P) L2
L4          3881 S (HISTONE DEACETYLASE) (P) INHIBIT?
L5         15569 S (HYDROXAMIC ACID) OR TRICHOSTATIN OR OXAMFLATIN OR (BISHYDROX
L6          1986 S L4 (P) L5
L7             2 S L3 (P) L5
L8             2 DUPLICATE REMOVE L7 (0 DUPLICATES REMOVED)

=> s cancer or antineoplastic or carcinoma or scarcoma or seminoma or myeloma or adenoma or adenoc
   4 FILES SEARCHED...
L9       4175688 CANCER OR ANTINEOPLASTIC OR CARCINOMA OR SCARCOMA OR SEMINOMA
                 OR MYELOMA OR ADENOMA OR ADENOCARCINOMA OR MALIGNANT OR LYMPHOMA
                  OR LEUKEMIA OR MELANOMA

=> s l7 (p) l9
L10            0 L7 (P) L9

=> d his

     (FILE 'HOME' ENTERED AT 10:30:45 ON 01 JUN 2002)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     10:31:15 ON 01 JUN 2002
L1          3344 S (DNA METHYLATION) (P) INHIBIT?
L2         31295 S CYTIDINE OR DECITABINE
L3           100 S L1 (P) L2
L4          3881 S (HISTONE DEACETYLASE) (P) INHIBIT?
L5         15569 S (HYDROXAMIC ACID) OR TRICHOSTATIN OR OXAMFLATIN OR (BISHYDROX
L6          1986 S L4 (P) L5
L7             2 S L3 (P) L5
L8             2 DUPLICATE REMOVE L7 (0 DUPLICATES REMOVED)
L9       4175688 S CANCER OR ANTINEOPLASTIC OR CARCINOMA OR SCARCOMA OR SEMINOMA
L10            0 S L7 (P) L9

=> s doxorubcin or daunorubicin or epirubcin or idarubicin or anthracenedione or (mitomycin C) or
L11      174434 DOXORUBCIN OR DAUNORUBICIN OR EPIRUBCIN OR IDARUBICIN OR ANTHRAC
                ENEDIONE OR (MITOMYCIN C) OR BLEOMYCIN OR DACTINOMYCIN OR PLICAT
                OMYCIN

=> s (l1 or l2) and (l4 or l5) and (l9 or l11)
L12          133 (L1 OR L2) AND (L4 OR L5) AND (L9 OR L11)
```

```
=> duplicate remove l12
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L12
L13          50 DUPLICATE REMOVE L12 (83 DUPLICATES REMOVED)

=> s l13 (p) inhibit?
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L80 (P) INHIBIT?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L82 (P) INHIBIT?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L84 (P) INHIBIT?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L86 (P) INHIBIT?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L88 (P) INHIBIT?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L90 (P) INHIBIT?'
L14          49 L13 (P) INHIBIT?

=> s l3 and l6
L15           2 L3 AND L6

=> s l15 not l7
L16           0 L15 NOT L7

=> d his

     (FILE 'HOME' ENTERED AT 10:30:45 ON 01 JUN 2002)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     10:31:15 ON 01 JUN 2002
L1         3344 S (DNA METHYLATION) (P) INHIBIT?
L2        31295 S CYTIDINE OR DECITABINE
L3          100 S L1 (P) L2
L4         3881 S (HISTONE DEACETYLASE) (P) INHIBIT?
L5        15569 S (HYDROXAMIC ACID) OR TRICHOSTATIN OR OXAMFLATIN OR (BISHYDROX
L6         1986 S L4 (P) L5
L7            2 S L3 (P) L5
L8            2 DUPLICATE REMOVE L7 (0 DUPLICATES REMOVED)
L9      4175688 S CANCER OR ANTINEOPLASTIC OR CARCINOMA OR SCARCOMA OR SEMINOMA
L10           0 S L7 (P) L9
L11      174434 S DOXORUBCIN OR DAUNORUBICIN OR EPIRUBCIN OR IDARUBICIN OR ANTH
L12         133 S (L1 OR L2) AND (L4 OR L5) AND (L9 OR L11)
L13          50 DUPLICATE REMOVE L12 (83 DUPLICATES REMOVED)
L14          49 S L13 (P) INHIBIT?
L15           2 S L3 AND L6
L16           0 S L15 NOT L7

=> s l7 and l11
L17           0 L7 AND L11

=> s (dna methylation) or (histone deaceytlase)
L18       27300 (DNA METHYLATION) OR (HISTONE DEACEYTLASE)

=> s (dna methylation) (p) (histone deaceytlase)
L19           0 (DNA METHYLATION) (P) (HISTONE DEACEYTLASE)

=> d l14 1-49 ibib abs

L14  ANSWER 1 OF 49      MEDLINE
ACCESSION NUMBER:    2002287776      IN-PROCESS
DOCUMENT NUMBER:     22022237   PubMed ID: 12001099
TITLE:               Silencing of pi-class glutathione S-transferase in MDA PCa
                     2a and MDA PCa 2b cells.
AUTHOR:              Vidanes Genevieve M; Paton Vince; Wallen Eric; Peehl Donna
                     M; Navone Nora; Brooks James D
CORPORATE SOURCE:    Department of Urology, Stanford University Medical Center,
                     Pasteur Drive, Stanford, California.
SOURCE:              PROSTATE, (2002 Jun 1) 51 (4) 225-30.
```

Journal code: 8101368. ISSN: 0270-4137.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020528
Last Updated on STN: 20020528

AB BACKGROUNDLoss of expression of the glutathione S-transferase-pi (GSTP1) is the most common genetic alteration described in human prostate ***cancer*** , occurring in virtually all tumors regardless of grade or stage. Of the available human prostate ***cancer*** cell lines, only LNCaP mirrors this phenotype. We investigated whether the prostate ***cancer*** cell lines MDA PCa 2a and MDA PCa 2b share this phenotype.METHODSGSTP1 protein and mRNA levels were assessed in the MDA PCa 2a and MDA PCa 2b cell lines by Western and Northern blot. ***DNA*** ***methylation*** was evaluated by Southern blot analysis of genomic DNA digested with the methylation-sensitive restriction enzymes BssHII, NotI, and SacII. Re-expression of GSTP1 was determined by RT-PCR following treatment with 5-azacytidine, a DNA methyltransferase ***inhibitor*** , and/or the ***histone*** ***deacetylase*** ***inhibitor*** ***trichostatin*** A (TSA).RESULTSLike all human prostatic ***carcinomas*** in vivo, both the MDA PCa 2a and 2b cell lines lack protein and mRNA expression of GSTP1. This lack of expression is associated with methylation in the GSTP1 gene promoter. Treatment with the methyltransferase ***inhibitor*** 5-azacytidine resulted in re-expression of GSTP1. By itself, TSA did not result in re-expression of GSTP1, nor did it augment expression induced by 5-azacytidine.CONCLUSIONSMDA PCa 2a and 2b appear to be useful models of human prostatic ***carcinoma*** in that they lack expression of GSTP1 due to gene silencing via promoter methylation. ***Inhibition*** of histone acetylation does not appear to affect GSTP1 expression. Prostate 51: 225-230, 2002.

L14 ANSWER 2 OF 49 MEDLINE
ACCESSION NUMBER: 2002241174 IN-PROCESS
DOCUMENT NUMBER: 21975197 PubMed ID: 11850427
TITLE: Maintenance of Integrated Proviral Gene Expression Requires Brm, a Catalytic Subunit of SWI/SNF Complex.
AUTHOR: Mizutani Taketoshi; Ito Taiji; Nishina Mitsue; Yamamichi Nobutake; Watanabe Akiko; Iba Hideo
CORPORATE SOURCE: Division of Host-Parasite Interaction, Department of Microbiology and Immunology, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 May 3) 277 (18) 15859-64.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020430
Last Updated on STN: 20020430

AB We show here that murine ***leukemia*** virus-based retrovirus vector transgene expression is rapidly silenced in human tumor cell lines lacking expression of Brm, a catalytic subunit of the SWI/SNF chromatin remodeling complex, even though these vectors can successfully enter, integrate, and initiate transcription. We detected this gene silencing as a reduction in the ratio of cells expressing the exogenous gene rather than a reduction in the average expression levels, indicating that down-regulation occurs in an all-or-none manner. Retroviral gene expression was protected from silencing and maintained in Brm-deficient host cells by exogenous expression of Brm but not BRG1, an alternative ATPase subunit in the SWI/SNF complex. Introduction of exogenous Brm to these cells suppressed recruitment of protein complexes containing YY1 and ***histone*** ***deacetylase*** (HDAC) 1 and 2 to the 5'-long terminal repeat region of the integrated provirus, leading to the enhancement of acetylation of specific lysine residues in histone H4 located in this region. Consistent with these observations, treatment of Brm-deficient cells with HDAC ***inhibitors*** but not ***DNA*** ***methylation*** ***inhibitors*** suppressed retroviral gene silencing. These results

suggest that the Brm-containing SWI/SNF complex subfamily (trithorax-G) and a complex including YY1 and HDACs (Polycomb-G) counteract each other to maintain transcription of exogenously introduced genes.

L14 ANSWER 3 OF 49 MEDLINE
ACCESSION NUMBER: 2002134134 MEDLINE
DOCUMENT NUMBER: 21853694 PubMed ID: 11865062
TITLE: Precipitous release of methyl-CpG binding protein 2 and histone deacetylase 1 from the methylated human multidrug resistance gene (MDR1) on activation.
AUTHOR: El-Osta Assam; Kantharidis Phillip; Zalcberg John R; Wolffe Alan P
CORPORATE SOURCE: Sir Donald & Lady Trescowthick Research Laboratories, Peter MacCallum Cancer Institute, St. Andrews Place, East Melbourne, Victoria 3002, Australia.. s.el-osta@pmci.unimelb.edu.au
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2002 Mar) 22 (6) 1844-57.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020301
Last Updated on STN: 20020313
Entered Medline: 20020312

AB Overexpression of the human multidrug resistance gene 1 (MDR1) is a negative prognostic factor in ***leukemia*** . Despite intense efforts to characterize the gene at the molecular level, little is known about the genetic events that switch on gene expression in P-glycoprotein-negative cells. Recent studies have shown that the transcriptional competence of MDR1 is often closely associated with ***DNA*** ***methylation*** . Chromatin remodeling and modification targeted by the recognition of methylated DNA provide a dominant mechanism for transcriptional repression. Consistent with this epigenetic model, interference with DNA methyltransferase and ***histone*** ***deacetylase*** activity alone or in combination can reactivate silent genes. In the present study, we used chromatin immunoprecipitation to monitor the molecular events involved in the activation and repression of MDR1. ***Inhibitors*** of DNA methyltransferase (5-azacytidine [5aC]) and ***histone*** ***deacetylase*** (***trichostatin*** A [TSA]) were used to examine gene transcription, promoter methylation status, and the chromatin determinants associated with the MDR1 promoter. We have established that methyl-CpG binding protein 2 (MeCP2) is involved in methylation-dependent silencing of human MDR1 in cells that lack the known transcriptional repressors MBD2 and MBD3. In the repressed state the MDR1 promoter is methylated and assembled into chromatin enriched with MeCP2 and deacetylated histone. TSA induced significant acetylation of histones H3 and H4 but did not activate transcription. 5aC induced DNA demethylation, leading to the release of MeCP2, promoter acetylation, and partial relief of repression. MDR1 expression was significantly increased following combined 5aC and TSA treatments. ***Inhibition*** of ***histone*** ***deacetylase*** is not an overriding mechanism in the reactivation of methylated MDR1. Our results provide us with a clearer understanding of the molecular mechanism necessary for repression of MDR1.

L14 ANSWER 4 OF 49 MEDLINE
ACCESSION NUMBER: 2002050867 MEDLINE
DOCUMENT NUMBER: 21634700 PubMed ID: 11774283
TITLE: Prostasin serine protease ***inhibits*** breast ***cancer*** invasiveness and is transcriptionally regulated by promoter ***DNA*** ***methylation*** .
AUTHOR: Chen Li-Mei; Chai Karl X
CORPORATE SOURCE: Department of Molecular Biology and Microbiology, University of Central Florida, 4000 Central Florida Boulevard, Orlando, FL 32816-2360, USA.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (2002 Jan 20) 97 (3) 323-9.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020128
Entered Medline: 20020124

AB We have shown that prostasin serine protease is downregulated in high-grade prostate tumors and ***inhibits*** invasiveness of prostate ***cancer*** cell lines upon enforced reexpression. In our study, prostasin mRNA and protein were shown to be expressed in normal human mammary epithelial cells (NHMEC), the poorly invasive breast ***carcinoma*** cell line MCF-7 and the nonmetastatic breast ***carcinoma*** cell line MDA-MB-453, but absent in highly invasive and metastatic breast ***carcinoma*** cell lines MDA-MB-231 and MDA-MB-435s. Enforced reexpression of prostasin in MDA-MB-231 and MDA-MB-435s reduced the in vitro invasiveness of either cell line by 50%. Examination of the prostasin gene promoter and first exon revealed a GC-enriched region that contains transcription regulatory elements. The promoter and exon 1 region of the prostasin gene was investigated for ***DNA*** ***methylation*** in NHMEC and the ***carcinoma*** cell lines. The results revealed a methylation pattern that correlates with prostasin expression in these cells. Demethylation coupled with ***histone*** ***deacetylase*** ***inhibition*** resulted in reactivated expression of the prostasin mRNA in MDA-MB-231 and MDA-MB-435s cells. These results suggest that prostasin expression in breast ***cancer*** cells may be regulated by ***DNA*** ***methylation*** and that an absence of prostasin expression may contribute to breast ***cancer*** invasiveness and metastatic potential.

L14 ANSWER 5 OF 49 MEDLINE
ACCESSION NUMBER: 2002000145 MEDLINE
DOCUMENT NUMBER: 21624913 PubMed ID: 11753657
TITLE: Increased expression of unmethylated CDKN2D by 5-aza-2'-deoxycytidine in human lung ***cancer*** cells.
AUTHOR: Zhu W G; Dai Z; Ding H; Srinivasan K; Hall J; Duan W; Villalona-Calero M A; Plass C; Otterson G A
CORPORATE SOURCE: Division of Hematology/Oncology, Department of Internal Medicine, The Ohio State University-Comprehensive Cancer Center, Columbus, OH 43210, USA.
CONTRACT NUMBER: P30 CA16058 (NCI)
SOURCE: ONCOGENE, (2001 Nov 22) 20 (53) 7787-96.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20020102
Last Updated on STN: 20020125
Entered Medline: 20020110

AB DNA hypermethylation of CpG islands in the promoter region of genes is associated with transcriptional silencing. Treatment with hypo-methylating agents can lead to expression of these silenced genes. However, whether ***inhibition*** of ***DNA*** ***methylation*** influences the expression of unmethylated genes has not been extensively studied. We analysed the methylation status of CDKN2A and CDKN2D in human lung ***cancer*** cell lines and demonstrated that the CDKN2A CpG island is methylated, whereas CDKN2D is unmethylated. Treatment of cells with 5-aza-2'-deoxycytidine (5-Aza-CdR), an ***inhibitor*** of DNA methyltransferase 1, induced a dose and duration dependent increased expression of both p16(INK4a) and p19(INK4d), the products of CDKN2A and CDKN2D, respectively. These data indicate that global DNA demethylation not only influences the expression of methylated genes but also of unmethylated genes. Histone acetylation is linked to methylation induced transcriptional silencing. Depsipeptide, an ***inhibitor*** of ***histone*** ***deacetylase*** , acts synergistically with 5-Aza-CdR in inducing expression of p16(INK4a) and p19(INK4d). However, when cells were treated with higher concentrations of 5-Aza-CdR and depsipeptide, p16(INK4a) expression was decreased together with significant suppression of cell growth. Interestingly, p19(INK4d) expression was enhanced even more by the higher concentrations of 5-Aza-CdR and depsipeptide. Our data

suggest that p19(INK4d) plays a distinct role from other INK4 family members in response to the c[redacted]toxicity induced by ***inhib[redacted]on*** of ***DNA*** ***methylation*** and histone deacetylation.

L14 ANSWER 6 OF 49 MEDLINE
ACCESSION NUMBER: 2001673186 MEDLINE
DOCUMENT NUMBER: 21575860 PubMed ID: 11719467
TITLE: Heterogeneous transforming growth factor (TGF)-beta unresponsiveness and loss of TGF-beta receptor type II expression caused by histone deacetylation in lung ***cancer*** cell lines.
AUTHOR: Osada H; Tatematsu Y; Masuda A; Saito T; Sugiyama M; Yanagisawa K; Takahashi T
CORPORATE SOURCE: Division of Molecular Oncology, Aichi Cancer Center Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan.. hosada@aichi-cc.jp
SOURCE: CANCER RESEARCH, (2001 Nov 15) 61 (22) 8331-9. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011126
Last Updated on STN: 20020123
Entered Medline: 20011212

AB Transforming growth factor (TGF)-beta strongly ***inhibits*** epithelial cell proliferation. Alterations of TGF-beta signaling are thought to play a role in tumorigenesis. We show in the present study that most lung ***cancer*** cell lines have lost the growth-***inhibitory*** response to TGF-beta signal, and that those with TGF-beta unresponsiveness can be divided into two major groups, TGF-beta type II receptor (TGFbetaRII)(+)/Smad7(+) and TGFbetaRII(-)/Smad7(-), suggesting the heterogeneous mechanisms underlying the TGF-beta responsiveness. The mechanism of the loss of TGFbetaRII expression of the latter group was further studied, identifying aberrant ***DNA*** ***methylation*** of the promoter region in a limited fraction of cell lines. Interestingly, we found that the alteration of chromatin structure because of histone deacetylation may also be involved, showing a good correlation with loss of TGFbetaRII expression. This notion was supported by the findings of a restriction enzyme accessibility assay, of a chromatin immunoprecipitation assay with anti-acetyl histone antibodies, and of an in vivo induction of TGFbetaRII expression by ***histone*** ***deacetylase*** ***inhibitors*** including ***trichostatin*** A (TSA) and sodium butyrate. In vitro induction of TGFbetaRII promoter reporter activity by TSA was also detected and found to require the CCAAT box within the -127/-75 region. A positive regulatory mechanism for TGFbetaRII expression in a TGF-beta-expressing cell line was also investigated, and a TPA-responsive element (TRE)-like motif, TRE2, was detected in addition to the previously reported TRE-like motif Y element in the positive regulatory region. Alterations in two discrete proteins interacting with these two TRE-like motifs were also suspected of being involved in the loss of TGFbetaRII expression. This is the first study to demonstrate that, in addition to the TSA-responsive region and TRE2 motif in the TGFbetaRII promoter, the alteration of histone deacetylation may be involved in the loss of TGFbetaRII expression in lung ***cancer*** cell lines.

L14 ANSWER 7 OF 49 MEDLINE
ACCESSION NUMBER: 2001643915 MEDLINE
DOCUMENT NUMBER: 21552774 PubMed ID: 11696424
TITLE: Caveolin-1 is down-regulated in human ovarian ***carcinoma*** and acts as a candidate tumor suppressor gene.
AUTHOR: Wiechen K; Diatchenko L; Agoulnik A; Scharff K M; Schober H; Arlt K; Zhumabayeva B; Siebert P D; Dietel M; Schafer R; Sers C
CORPORATE SOURCE: Institute of Pathology, Charite, Humboldt University Berlin, Berlin, Germany.
SOURCE: AMERICAN JOURNAL OF PATHOLOGY, (2001 Nov) 159 (5) 1635-43. Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011107
Last Updated on STN: 20020123
Entered Medline: 20011207

AB To identify novel markers differentially expressed in ovarian ***cancer*** versus normal ovary, we hybridized microarrays with cDNAs derived from normal human ovaries and advanced stage ovarian ***carcinomas*** . This analysis revealed down-regulation of the caveolin-1 gene (CAV1) in ovarian ***carcinoma*** samples. Suppression of CAV1 in ovarian ***carcinomas*** was confirmed using a tumor tissue array consisting of 68 cDNA pools from different matched human tumor and normal tissues. Immunohistochemistry demonstrated expression of caveolin-1 in normal and benign ovarian epithelial cells, but loss of expression in serous ovarian ***carcinomas*** . In low-grade ***carcinomas*** , redistribution of caveolin-1 from a membrane-associated pattern observed in normal epithelium to a cytoplasmic localization pattern was observed. No expression of caveolin-1 was detectable in four of six ovarian ***carcinoma*** cell lines investigated. In SKOV-3 and ES-2 ***carcinoma*** cells, which express high levels of the caveolin-1 protein, phosphorylation of the 22-kd caveolin-1 isoform was detected. ***Inhibition*** of both ***DNA*** ***methylation*** and histone deacetylation using 5-aza-2'deoxycytidine and ***Trichostatin*** A, respectively, relieves down-regulation of caveolin-1 in OAW42 and OVCAR-3 cells which is in part mediated by direct regulation at the mRNA level. Expression of CAV1 in the ovarian ***carcinoma*** cell line OVCAR-3, resulted in suppression of tumor cell survival in vitro, suggesting that the CAV1 gene is likely to act as a tumor suppressor gene in human ovarian epithelium.

L14 ANSWER 8 OF 49 MEDLINE
ACCESSION NUMBER: 2001608502 MEDLINE
DOCUMENT NUMBER: 21539676 PubMed ID: 11683489
TITLE: Inactivation of retinoic acid receptor beta by promoter CpG hypermethylation in gastric ***cancer*** .
AUTHOR: Hayashi K; Yokozaki H; Goodison S; Oue N; Suzuki T; Lotan R; Yasui W; Tahara E
CORPORATE SOURCE: First Department of Pathology, Hiroshima University School of Medicine, Japan.. etahara@cisnet.or.jp
CONTRACT NUMBER: DE11906 (NIDCR)
p101-CA52051 (NCI)
SOURCE: DIFFERENTIATION, (2001 Aug) 68 (1) 13-21.
Journal code: 0401650. ISSN: 0301-4681.
PUB. COUNTRY: Germany: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20011102
Last Updated on STN: 20020320
Entered Medline: 20020319

AB Inactivation of nuclear retinoic acid receptor beta (RARbeta) expression is implicated in tumorigenesis. We hypothesized that loss of RARbeta in gastric ***cancer*** cells may occur as a result of multiple factors, including epigenetic modifications which alter RARbeta promoter chromatin structure. We examined hypermethylation of CpG islands present in the RARbeta promoter by methylation-specific PCR and the expression of RARbeta in gastric ***cancer*** cell lines and tissues. Three (MKN-28, -45 and -74) out of eight gastric ***cancer*** cell lines had a loss of RAR expression associated with promoter methylation. RARbeta expression was retrieved in these cell lines by treatment with 5-azacytidine or by the ***histone*** ***deacetylase*** ***inhibitor*** ***trichostatin*** A. Promoter hypermethylation was detected in 64% (7/11) of gastric ***carcinoma*** tissues with reduced expression of RARbeta, whereas it was detected in 22% (2/9) of tumors with retained RARbeta expression. To investigate the functions of exogenous RARbeta in gastric ***cancer*** cells, we transfected a retroviral RARbeta expression vector (LNSbeta) into MKN-28 cells that have hypermethylation of the RARbeta promoter. Overexpression of RAR in MKN-28 cells appeared to regulate the expression of DNA methyltransferase and DNA demethylase and

the acetylation of hitone H4. These results suggest that the transcriptional inactivation of the RARbeta by promoter CpG hypermethylation is frequently associated with gastric ***carcinoma*** . Our data also suggests that ***DNA*** ***methylation*** plays a pivotal role in establishing and maintaining an inactive state of RARbeta by rendering the chromatin structure inaccessible to the transcription machinery.

L14 ANSWER 9 OF 49 MEDLINE
ACCESSION NUMBER: 2001492419 MEDLINE
DOCUMENT NUMBER: 21417721 PubMed ID: 11504918
TITLE: CmC(A/T)GG DNA methylation in mature B cell ***lymphoma*** gene silencing.
COMMENT: Comment in: Proc Natl Acad Sci U S A. 2001 Aug 28;98(18):10034-6
AUTHOR: Malone C S; Miner M D; Doerr J R; Jackson J P; Jacobsen S E; Wall R; Teitell M
CORPORATE SOURCE: Department of Microbiology and Immunology, Jonsson Comprehensive Cancer Center, University of California, Center for the Health Sciences, Los Angeles, CA 90095, USA.
CONTRACT NUMBER: CA74929 (NCI)
CA85841 (NCI)
T32CA09056 (NCI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2001 Aug 28) 98 (18) 10404-9.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010906
Last Updated on STN: 20011008
Entered Medline: 20011004

AB ***DNA*** ***methylation*** has been linked to gene silencing in ***cancer*** . Primary effusion ***lymphoma*** (PEL) and ***myeloma*** are lymphoid malignancies that arise from terminally differentiated B cells. Interestingly, PEL do not express immunoglobulins or most B lineage-specific genes. The B cell-specific B29 (Igbeta/CD79b) gene is silenced in PEL and some ***myelomas*** but is expressed in other normal and ***malignant*** B cells. B29 expression was reactivated in PEL by demethylating and ***histone*** ***deacetylase*** ***inhibiting*** treatments. Bisulfite sequencing revealed two types of ***DNA*** ***methylation*** in silenced B29 promoters: at conventional CpG and at CC(A/T)GG B29 promoter sites. The pattern of methylated CpG ((m)CpG) and C(m)C(A/T)GG B29 promoter methylation observed was similar to that recently reported for epigenetic silencing of an integrated retrovirus. Methylation of C(m)C(A/T)GG sites in the B29 promoter significantly repressed in vivo transcriptional activity. Also, methylation of a central conserved C(m)CTGG B29 promoter site blocked the binding of early B cell factor. This methylated motif formed DNA-protein complexes with nuclear extracts from all cell types examined. Therefore, C(m)C(A/T)GG methylation may represent an important type of epigenetic marker on mammalian DNA that impacts transcription by altering DNA-protein complex formation.

L14 ANSWER 10 OF 49 MEDLINE
ACCESSION NUMBER: 2001455353 MEDLINE
DOCUMENT NUMBER: 21392487 PubMed ID: 11501578
TITLE: Role of DNA methylation and histone acetylation in steroid receptor expression in breast ***cancer*** .
AUTHOR: Yan L; Yang X; Davidson N E
CORPORATE SOURCE: Johns Hopkins Oncology Center, Baltimore, Maryland 21231, USA.
CONTRACT NUMBER: 2-T32CA09110 (NCI)
CA78352 (NCI)
P50CA88843 (NCI)
SOURCE: JOURNAL OF MAMMARY GLAND BIOLOGY AND NEOPLASIA, (2001 Apr) 6 (2) 183-92. Ref: 73
Journal code: 9601804. ISSN: 1083-3021.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20010815
Last Updated on STN: 20020122
Entered Medline: 20011220

AB ***DNA*** ***methylation*** is an epigenetic modification that is associated with transcriptional silencing of gene expression in mammalian cells. Hypermethylation of the promoter CpG islands contributes to the loss of gene function of several tumor related genes, including estrogen receptor a (ER) and progesterone receptor (PR). Gene expression patterns are also heavily influenced by changes in chromatin structure during transcription. Indeed both the predominant mammalian DNA methyltransferase (DNMTI), and the ***histone*** ***deacetylases*** (HDACs) play crucial roles in maintaining transcriptionally repressive chromatin by forming suppressive complexes at replication foci. These new findings suggest that epigenetic changes might play a crucial role in gene inactivation in breast ***cancer*** . Further, ***inhibition*** of ***DNA*** ***methylation*** and histone deacetylation might be a therapeutic strategy in breast ***cancer*** , especially for those ***cancers*** with ER and PR negative phenotypes.

L14 ANSWER 11 OF 49 MEDLINE
ACCESSION NUMBER: 2001442906 MEDLINE
DOCUMENT NUMBER: 21380725 PubMed ID: 11488527
TITLE: ***Antineoplastic*** action of 5-aza-2'-deoxycytidine and ***histone*** ***deacetylase*** ***inhibitor*** and their effect on the expression of retinoic acid receptor beta and estrogen receptor alpha genes in breast ***carcinoma*** cells.
AUTHOR: Bovenzi V; Momparler R L
CORPORATE SOURCE: Department de pharmacologie, Universite de Montreal, Quebec, Canada.
SOURCE: CANCER CHEMOTHERAPY AND PHARMACOLOGY, (2001 Jul) 48 (1) 71-6.
Journal code: C9S; 7806519. ISSN: 0344-5704.
PUB. COUNTRY: Germany: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010903
Entered Medline: 20010830

AB PURPOSE: During tumorigenesis several ***cancer*** -related genes can be silenced by aberrant methylation. In many cases these silenced genes can be reactivated by exposure to the ***DNA*** ***methylation*** ***inhibitor*** , 5-aza-2'-deoxycytidine (5-AZA-CdR). Histone acetylation also plays a role in the control of expression of some genes. The aim of this study was to determine the ***antineoplastic*** activities of 5-AZA-CdR and ***trichostatin*** A (TSA), either administered alone or in combination. in MDA-MB-231 breast ***carcinoma*** cells. The effects of these drugs (alone and in combination) on the expression of the tumor suppressor gene, retinoic acid receptor (RAR beta) and of the estrogen receptor alpha gene (ER alpha), whose expression is lost in the cell line used in the study, were also investigated. METHODS: MDA-MB-231 cells were treated with 5-AZA-CdR and TSA and the antitumor activity of these drugs was determined by clonogenic assay. Total RNA was extracted from the treated cells and RT-PCR was used to determine the effect of the treatment on the expression of RAR beta and ER alpha. Methylation-sensitive PCR analysis was used to confirm that lack of expression of both genes was due to hypermethylation of their promoter regions. A single nucleotide primer extension assay was also used to quantify the reduction in ***DNA*** ***methylation*** following drug treatment. RESULTS: Both 5-AZA-CdR and TSA alone showed significant ***antineoplastic*** activity. The combination of the two drugs was synergistic with respect to MDA-MB-231 cell kill. 5-AZA-CdR alone weakly activated the expression of both RAR beta and ER alpha. TSA alone only activated RAR beta, but not ER alpha. The combination of these agents appeared to produce a greater activation of both genes. CONCLUSIONS: The interesting interaction between

5-AZA-CdR and TSA in both cell kill and ***cancer*** -related gene reactivation provides a rationale for the use of ***inhibitors*** of ***DNA*** ***methylation*** and histone deacetylation in combination for the chemotherapy of breast ***cancer*** .

L14 ANSWER 12 OF 49 MEDLINE
ACCESSION NUMBER: 2001369124 MEDLINE
DOCUMENT NUMBER: 21153104 PubMed ID: 11230184
TITLE: Association of acetylated histones with paternally expressed genes in the Prader--Willi deletion region.
AUTHOR: Fulmer-Smentek S B; Francke U
CORPORATE SOURCE: Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, CA 94305-5323, USA.
SOURCE: HUMAN MOLECULAR GENETICS, (2001 Mar 15) 10 (6) 645-52. Journal code: BRC; 9208958. ISSN: 0964-6906.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010702
Last Updated on STN: 20010702
Entered Medline: 20010628

AB Imprinted genes within the Prader-Willi/Angelman syndrome region of human chromosome 15q11-q13 are regulated by a mechanism involving allele-specific ***DNA*** ***methylation*** . Since transcriptional regulation by ***DNA*** ***methylation*** involves histone deacetylation, we explored whether differences in histone acetylation exist between the two parental alleles of SNRPN and other paternally expressed genes in the region by using a chromatin immunoprecipitation assay with antibodies against acetylated histones H3 and H4. SNRPN exon 1, which is methylated on the silent maternal allele, was associated with acetylated histones on the expressed paternal allele only. SNRPN intron 7, which is methylated on the paternal allele, was not associated with acetylated histones on either allele. The paternally expressed genes NDN, IPW, PWCR1 and MAGEL2 were not associated with acetylated histones on either allele. Treatment of the lymphoblastoid cells with ***trichostatin*** A, a ***histone*** ***deacetylase*** ***inhibitor*** , did not result in any changes to SNRPN expression or association of acetylated histones with exon 1. Treatment with 5-aza-deoxycytidine (5-aza-dC), which ***inhibits*** ***DNA*** ***methylation*** , resulted in activation of SNRPN expression from the maternal allele, but was not accompanied by acetylation of histones. Our finding of allele-specific association of acetylated histones with the SNRPN exon 1 region, which encompasses the imprinting center, suggests that histone acetylation at this site may be important for regulation of SNRPN and of other paternally expressed genes in the region. On the silent allele, 5-aza-dC treatment altered SNRPN expression, but not association with acetylated histones, suggesting that histone acetylation is a secondary event in the process of gene reactivation by CpG demethylation.

L14 ANSWER 13 OF 49 MEDLINE
ACCESSION NUMBER: 2001231597 MEDLINE
DOCUMENT NUMBER: 21221066 PubMed ID: 11309512
TITLE: Selective association of the methyl-CpG binding protein MBD2 with the silent p14/p16 locus in human neoplasia.
AUTHOR: Magdinier F; Wolffe A P
CORPORATE SOURCE: Laboratory of Molecular Embryology, National Institute of Child Health and Human Development, National Institutes of Health, Building 18T, Room 106, Bethesda, MD 20892, USA.. FrederiqueM@intra.niddk.nih.gov
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2001 Apr 24) 98 (9) 4990-5. Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010529
Last Updated on STN: 20010529
Entered Medline: 20010521

AB ***DNA*** ***methylation*** of tumor suppressor genes is a common feature of human ***cancer*** . The cyclin-dependent kinase ***inhibitor*** gene p16/Ink4A is hypermethylated in a wide range of ***malignant*** tissues and the p14/ARF gene located 20 kb upstream on chromosome 9p21 is also methylated in ***carcinomas*** . p14/ARF (ARF, alternative reading frame) does not ***inhibit*** the activities of cyclins or cyclin-dependent kinase complexes; however, the importance of the two gene products in the etiology of ***cancer*** resides in their involvement in two major cell cycle regulatory pathways: p53 and the retinoblastoma protein, Rb, respectively. Distinct first exons driven from separate promoters are spliced onto the common exons 2 and 3 and the resulting proteins are translated in different reading frames. Both genes are expressed in normal cells but can be alternatively or coordinately silenced when their CpG islands are hypermethylated. Herein, we examined the presence of methyl-CpG binding proteins associated with aberrantly methylated promoters, the distribution of acetylated histones H3 and H4 by chromatin immunoprecipitation assays, and the effect of chemical treatment with 5-aza-2'-deoxycytidine (5aza-dC) and ***trichostatin*** A on gene induction in colon cell lines by quantitative reverse transcriptase-PCR. We observed that the methyl-CpG binding protein MBD2 is targeted to methylated regulatory regions and excludes the acetylated histones H3 and H4, resulting in a localized inactive chromatin configuration. When methylated, the genes can be induced by 5aza-dC but the combined action of 5aza-dC and ***trichostatin*** A results in robust gene expression. Thus, methyl-CpG binding proteins and ***histone*** ***deacetylases*** appear to cooperate in vivo, with a dominant effect of ***DNA*** ***methylation*** toward histone acetylation, and repress expression of tumor suppressor genes hypermethylated in ***cancers*** .

L14 ANSWER 14 OF 49 MEDLINE
ACCESSION NUMBER: 2001184179 MEDLINE
DOCUMENT NUMBER: 21139057 PubMed ID: 11245429
TITLE: DNA methyltransferase ***inhibition*** enhances apoptosis induced by ***histone*** ***deacetylase*** ***inhibitors*** .
AUTHOR: Zhu W G; Lakshmanan R R; Beal M D; Otterson G A
CORPORATE SOURCE: Department of Internal Medicine and the Comprehensive Cancer Center, The Ohio State University, Columbus 43210-1240, USA.
CONTRACT NUMBER: 1 R25 CA82351 (NCI)
P30 CA16058 (NCI)
SOURCE: CANCER RESEARCH, (2001 Feb 15) 61 (4) 1327-33.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010329

AB Histone acetylation has long been associated with transcriptional activation, whereas conversely, deacetylation of histones is associated with gene silencing and transcriptional repression. Here we report that ***inhibitors*** of ***histone*** ***deacetylase*** (HDAC), depsipeptide and ***trichostatin*** A, induce apoptotic cell death in human lung ***cancer*** cells as demonstrated by DNA flow cytometry and Western immunoblot to detect cleavage of poly(ADP-ribose) polymerase. This HDAC ***inhibitorinduced*** apoptosis is greatly enhanced in the presence of the DNA methyltransferase ***inhibitor*** , 5-aza-2'-deoxycytidine (DAC). The HDAC ***inhibitor*** -induced apoptosis appears to be p53 independent, because no change in apoptotic cell death was observed in H1299 cells that expressed exogenous wild-type p53 (H1299 cells express no endogenous p53 protein). To further investigate the mechanism of DAC-enhanced, HDAC ***inhibitor*** -induced apoptosis, we analyzed histone H3 and H4 acetylation by Western immunoblotting. Results showed that depsipeptide induced a dose-dependent acetylation of histones H3 and H4, which was greatly increased in DAC-pretreated cells. By analyzing the acetylation of specific lysine residues at the amino terminus of histone H4 (Ac-5, Ac-8, Ac-12, and Ac-16), we found that the enhancement of HDAC ***inhibitor*** -induced

acetylation of histones in the DAC-pretreated cells was not lysine site specific. These results demonstrate that ***DNA*** ***methylation*** status is an important determinant of apoptotic susceptibility to HDAC ***inhibitors*** .

L14 ANSWER 15 OF 49 MEDLINE
ACCESSION NUMBER: 2001153834 MEDLINE
DOCUMENT NUMBER: 21039633 PubMed ID: 11196471
TITLE: Mechanisms of epigenetic silencing of the c21 gene in Y1 adrenocortical tumor cells.
AUTHOR: Szyf M; Slack A D
CORPORATE SOURCE: Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada..
mszyf@pharma.mcgill.ca
SOURCE: ENDOCRINE RESEARCH, (2000 Nov) 26 (4) 921-30.
Journal code: EIH; 8408548. ISSN: 0743-5800.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010322

AB We utilized Y1 adrenocortical ***carcinoma*** cell line as a model system to dissect the events regulating epigenomic gene silencing in tumor cells. We show here that the chromatin structure of c21 gene is inactive in Y1 cells and that it could be reconfigured to an active form by either expressing antisense mRNA to DNA methyltransferase 1 (dnmt1) or an attenuator of Ras protooncogenic signaling hGAP. Surprisingly however, the known inducer of active chromatin structure the ***histone*** ***deacetylase*** ***inhibitor*** ***trichostatin*** A TSA fails to induce expression of c21. These results suggest that the primary cause of c21 gene silencing is independent of histone deacetylation. We present a model to explain the possible roles of the different components of the epigenome and the ***DNA*** ***methylation*** and demethylation machineries in silencing c21 gene expression.

L14 ANSWER 16 OF 49 MEDLINE
ACCESSION NUMBER: 2001124267 MEDLINE
DOCUMENT NUMBER: 21028083 PubMed ID: 11156387
TITLE: Transcriptional activation of estrogen receptor alpha in human breast ***cancer*** cells by ***histone*** ***deacetylase*** ***inhibition*** .
AUTHOR: Yang X; Ferguson A T; Nass S J; Phillips D L; Butash K A; Wang S M; Herman J G; Davidson N E
CORPORATE SOURCE: The Johns Hopkins Oncology Center, Johns Hopkins University, Baltimore, Maryland 21231, USA.
CONTRACT NUMBER: 2-T32CA09110 (NCI)
CA78352 (NCI)
SOURCE: CANCER RESEARCH, (2000 Dec 15) 60 (24) 6890-4.
Journal code: CNF. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010222

AB Recent findings have established a connection between ***DNA*** ***methylation*** and transcriptionally inactive chromatin characterized by deacetylated histones. Because the absence of estrogen receptor alpha (ERalpha) gene expression has been associated with aberrant methylation of its CpG island in a significant fraction of breast ***cancers*** , we tested whether ***histone*** ***deacetylase*** activity contributes to the transcriptional inactivation of the methylated ER gene in a panel of ER-negative human breast ***cancer*** cells. Treatment of these cells with ***trichostatin*** A, a specific ***histone*** ***deacetylase*** ***inhibitor*** , led to dose- and time-dependent re-expression of ER mRNA as detected by reverse transcription-PCR without alteration in ERalpha CpG island methylation. ***Trichostatin***

A-induced ER re-expression was associated with increased sensitivity to DNase I at the ER locus in MDA-MB-231 cells. These data implicate inactive chromatin mediated by histone deacetylation as a critical component of ER gene silencing in human breast ***cancer*** cells. Therefore, histone deacetylation may be a potential target for therapeutic intervention in the treatment of a subset of ER-negative breast ***cancers*** .

L14 ANSWER 17 OF 49 MEDLINE
ACCESSION NUMBER: 2001087236 MEDLINE
DOCUMENT NUMBER: 21020964 PubMed ID: 11140692
TITLE: Epigenetic regulation of androgen receptor gene expression in human prostate ***cancers*** .
AUTHOR: Nakayama T; Watanabe M; Suzuki H; Toyota M; Sekita N; Hirokawa Y; Mizokami A; Ito H; Yatani R; Shiraishi T
CORPORATE SOURCE: Second Department of Pathology, Mie University School of Medicine, Japan.
SOURCE: LABORATORY INVESTIGATION, (2000 Dec) 80 (12) 1789-96. Journal code: KZ4. ISSN: 0023-6837.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010118

AB Epigenetic mechanisms including ***DNA*** ***methylation*** and histone deacetylation are thought to play important roles in gene transcriptional inactivation. Heterogenous expression of androgen receptor (AR), which appears to be related to variable responses to endocrine therapy in prostate ***cancer*** (PCa) may also be due to epigenetic factors. The methylation status of the 5' CpG island of the AR in 3 prostate ***cancer*** cell lines and 10 primary and 14 hormone-refractory PCa samples was determined using the bisulfite PCR methods. In DU145, CpG-rich regions of the AR were hypermethylated. By an immunohistochemical analysis, only one PCa sample had no AR expression, the others being heterogenous. Bisulfite sequencing and methylation-specific PCR analysis showed aberrant methylation of AR 5'-regulatory region in 20% of 10 primary and 28% of 14 hormone-refractory PCa samples. To clarify the effect of epigenetic regulation on AR expression, we treated three prostate ***cancer*** cell lines with a demethylating agent, 5-aza-2'-deoxycytidine (azaC), and a ***histone*** ***deacetylase*** ***inhibitor*** , ***Trichostatin*** A (TSA). In DU145, re-expression of AR mRNA was detected after treatment with azaC and/or TSA. Our results suggest that epigenetic regulations including CpG methylation and histone acetylation may play important roles in the regulation of the AR.

L14 ANSWER 18 OF 49 MEDLINE
ACCESSION NUMBER: 2000501591 MEDLINE
DOCUMENT NUMBER: 20500518 PubMed ID: 11049023
TITLE: Novel therapeutic agents for the treatment of myelodysplastic syndromes.
AUTHOR: Cheson B D; Zwiebel J A; Dancey J; Murgo A
CORPORATE SOURCE: Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD 20892, USA.
SOURCE: SEMINARS IN ONCOLOGY, (2000 Oct) 27 (5) 560-77. Ref: 192
Journal code: UN5. ISSN: 0093-7754.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001102

AB Few chemotherapy agents have demonstrated activity in patients with myelodysplastic syndromes (MDS) and supportive management remains the standard of care. An increasing number of new drugs in development are

being directed at specific molecular or biological targets of these diseases. Topotecan, a topoi[redacted]merase I ***inhibitor*** , h[redacted] shown single-agent activity and is now being combined with other agents, including cytarabine. The aminothiol amifostine induces responses in about 30% of patients; however, its role is still being clarified. Agents that ***inhibit*** ***histone*** ***deacetylase*** and target DNA hypermethylation, thus permitting derepression of normal genes, include 5-azacytidine, ***decitabine*** , phenylbutyrate, and depsipeptide. Arsenic trioxide has demonstrated impressive activity in acute promyelocytic ***leukemia*** and preclinical data suggest the potential for activity in MDS. UCN-01 is a novel agent that ***inhibits*** protein kinase C and other protein kinases important for progression through the G1 and G2 phases of the cell cycle. Dolastatin-10 has extremely potent in vitro activity against a variety of tumor cell lines. Since its dose-limiting toxicities include myelosuppression, it is being studied in acute myelogenous ***leukemia*** (AML) and MDS. Ras may play a role in MDS, and activation of this gene and its signaling pathways may require farnesylation. Several farnesyl transferase ***inhibitors*** are now available for study in patients with MDS. An increasing body of data suggests a possible role for angiogenesis in MDS, and several antiangiogenesis agents are in clinical trials, including thalidomide, SU5416, and anti-vascular endothelial growth factor (VEGF) antibodies. Development of new drugs and regimens will be facilitated by recently developed standardized response criteria. Future clinical trials should focus on rational combinations of these agents and others with the goal of curing patients with MDS.

L14 ANSWER 19 OF 49 MEDLINE
ACCESSION NUMBER: 2000200625 MEDLINE
DOCUMENT NUMBER: 20200625 PubMed ID: 10734315
TITLE: Evidence of epigenetic changes affecting the chromatin state of the retinoic acid receptor beta2 promoter in breast ***cancer*** cells.
AUTHOR: Sirchia S M; Ferguson A T; Sironi E; Subramanyan S; Orlandi R; Sukumar S; Sacchi N
CORPORATE SOURCE: Laboratory of Human Genetics, Hospital San Paolo, University of Milan, Milan, Italy.
SOURCE: ONCOGENE, (2000 Mar 16) 19 (12) 1556-63. Journal code: ONC; 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000505
Last Updated on STN: 20000505
Entered Medline: 20000421

AB Retinoic acid (RA)-resistance in breast ***cancer*** cells has been associated with irreversible loss of retinoic acid receptor beta, RARbeta, gene expression. Search of the causes affecting RARbeta gene activity has been oriented at identifying possible differences either at the level of one of the RARbeta promoters, RARbeta2, or at regulatory factors. We hypothesized that loss of RARbeta2 activity occurs as a result of multiple factors, including epigenetic modifications, which can pattern RARbeta2 chromatin state. Using methylation-specific PCR, we found hypermethylation at RARbeta2 in a significant proportion of both breast ***cancer*** cell lines and primary breast tumors. Treatment of cells with a methylated RARbeta2 promoter, by means of the DNA methyltransferase ***inhibitor*** 5-Aza-2'-deoxycytidine (5-Aza-CdR), led to demethylation within RARbeta2 and expression of RARbeta indicating that ***DNA*** ***methylation*** is at least one factor, contributing to RARbeta inactivity. However, identically methylated promoters can differentially respond to RA, suggesting that RARbeta2 activity may be associated to different repressive chromatin states. This supposition is supported by the finding that the more stable repressive RARbeta2 state in the RA-resistant MDA-MB-231 cell line can be alleviated by the HDAC ***inhibitor*** , ***trichostatin*** A (TSA), with restoration of RA-induced RARbeta transcription. Thus, chromatin-remodeling drugs might provide a strategy to restore RARbeta activity, and help to overcome the hurdle of RA-resistance in breast ***cancer*** .

L14 ANSWER 20 OF 49 MEDLINE

ACCESSION NUMBER: 2000139833 MEDLINE
DOCUMENT NUMBER: 20139833 PubMed ID: 10676663
TITLE: Drg-1 as a differentiation-related, putative metastatic suppressor gene in human colon ***cancer*** .
AUTHOR: Guan R J; Ford H L; Fu Y; Li Y; Shaw L M; Pardee A B
CORPORATE SOURCE: Division of Gastroenterology, Brigham and Women's Hospital, Dana-Farber Cancer Institute, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: R0-1 CA61253 (NCI)
SOURCE: CANCER RESEARCH, (2000 Feb 1) 60 (3) 749-55.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000314
Last Updated on STN: 20000314
Entered Medline: 20000228

AB A gene related to cell differentiation was identified by differential display as a candidate suppressor of metastases in colon ***cancer*** . This gene, with a full-length cDNA of 3 kb, is expressed in normal colon and primary colon ***cancer*** tissues and cell lines but not in their metastatic counterparts. A GenBank search found that it is identical to a recently cloned gene, differentiation-related gene-1 (Drg-1), isolated from differentiated HT-29 colon ***cancer*** cells. Stable transfection of the SW620 metastatic colon ***cancer*** cell line with Drg-1 cDNA induced morphological changes consistent with differentiation and up-regulated the expression of several colonic epithelial cell differentiation markers (alkaline phosphatase, carcinoembryonic antigen, and E-cadherin). Moreover, the expression of Drg-1 is controlled by several known cell differentiation reagents, such as ligands of peroxisome proliferator-activated receptor gamma (troglitazone and BRL46593) and of retinoid X receptor (LG268), and ***histone*** ***deacetylase*** ***inhibitors*** (***trichostatin*** A, suberoylanilide ***hydroxamic*** ***acid*** , and tributyrin). A synergistic induction of Drg-1 expression was seen with the combination of tributyrin and a low dose of 5'-aza-2'-dexoycytidine (100 nM), an ***inhibitor*** of ***DNA*** ***methylation*** . Functional studies revealed that overexpression of Drg-1 in metastatic colon ***cancer*** cells reduced in vitro invasion through Matrigel and suppressed in vivo liver metastases in nude mice. We propose that Drg-1 suppresses colon ***cancer*** metastasis by inducing colon ***cancer*** cell differentiation and partially reversing the metastatic phenotype.

L14 ANSWER 21 OF 49 MEDLINE
ACCESSION NUMBER: 2000094963 MEDLINE
DOCUMENT NUMBER: 20094963 PubMed ID: 10629041
TITLE: Dynamic analysis of proviral induction and De Novo methylation: implications for a histone deacetylase-independent, methylation density-dependent mechanism of transcriptional repression.
AUTHOR: Lorincz M C; Schubeler D; Goeke S C; Walters M; Groudine M; Martin D I
CORPORATE SOURCE: Fred Hutchinson Cancer Research Center, University of Washington School of Medicine, Seattle, Washington, USA.. mlorincz@fhcrc.org
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 842-50.
Journal code: NGY; 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20000229
Entered Medline: 20000214

AB Methylation of cytosines in the CpG dinucleotide is generally associated with transcriptional repression in mammalian cells, and recent findings implicate histone deacetylation in methylation-mediated repression. Analyses of histone acetylation in in vitro-methylated transfected plasmids support this model; however, little is known about the

relationships among de novo ***DNA*** ***methylation*** transcriptional repression, [redacted] histone acetylation state. To [redacted]amine these relationships in vivo, we have developed a novel approach that permits the isolation and expansion of cells harboring expressing or silent retroviruses. MEL cells were infected with a Moloney murine ***leukemia*** virus encoding the green fluorescent protein (GFP), and single-copy, silent proviral clones were treated weekly with the ***histone*** ***deacetylase*** ***inhibitor*** ***trichostatin*** A or the ***DNA*** ***methylation*** ***inhibitor*** 5-azacytidine. Expression was monitored concurrently by flow cytometry, allowing for repeated phenotypic analysis over time, and proviral methylation was determined by Southern blotting and bisulfite methylation mapping. Shortly after infection, proviral expression was inducible and the reporter gene and proviral enhancer showed a low density of methylation. Over time, the efficacy of drug induction diminished, coincident with the accumulation of methyl-CpGs across the provirus. Bisulfite analysis of cells in which 5-azacytidine treatment induced GFP expression revealed measurable but incomplete demethylation of the provirus. Repression could be overcome in late-passage clones only by pretreatment with 5-azacytidine followed by ***trichostatin*** A, suggesting that partial demethylation reestablishes the ***trichostatin*** -inducible state. These experiments reveal the presence of a silencing mechanism which acts on densely methylated DNA and appears to function independently of ***histone*** ***deacetylase*** activity.

L14 ANSWER 22 OF 49 MEDLINE
ACCESSION NUMBER: 2000090221 MEDLINE
DOCUMENT NUMBER: 20090221 PubMed ID: 10626795
TITLE: DNA methylation analysis of the promoter region of the human telomerase reverse transcriptase (hTERT) gene.
AUTHOR: Devereux T R; Horikawa I; Anna C H; Annab L A; Afshari C A; Barrett J C
CORPORATE SOURCE: Laboratory of Molecular Carcinogenesis, National Institute of Environmental Health Sciences, NIH, Research Triangle Park, North Carolina 27709, USA.. devereux@niehs.nih.gov
SOURCE: CANCER RESEARCH, (1999 Dec 15) 59 (24) 6087-90. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20020420
Entered Medline: 20000124

AB The promoter of the hTERT gene encoding the catalytic subunit of telomerase was recently cloned and has a dense CG-rich CpG island, suggesting a role for methylation in regulation of hTERT expression. In this study, we have initiated the analysis of the regulation of hTERT expression by examining the methylation status of up to 72 CpG sites extending from 500 bases upstream of the transcriptional start site of the hTERT gene into the first exon in 37 cell lines. These cell lines represent a variety of cell and tissue types, including normal, immortalized, and ***cancer*** cell lines from lung, breast, and other tissues. Using bisulfite genomic sequencing, we did not find a generalized pattern of site-specific or region-specific methylation that correlated with expression of the hTERT gene: most of the hTERT-negative normal cells and about one-third of the hTERT-expressing cell lines had the unmethylated/hypomethylated promoter, whereas the other hTERT-expressing cell lines showed partial or total methylation of the promoter. The promoter of one hTERT-negative fibroblast cell line, SUSM-1, was methylated at all sites examined. Treatment of SUSM-1 cells with the demethylating agent 5-aza-2'-deoxycytidine and the ***histone*** ***deacetylase*** ***inhibitor*** ***trichostatin*** A induced the cells to express hTERT, suggesting a potential role for ***DNA*** ***methylation*** and/or histone deacetylation in negative regulation of hTERT. This study indicates that there are multiple levels of regulation of hTERT expression in CpG island methylation-dependent and -independent manners.

L14 ANSWER 23 OF 49 MEDLINE

ACCESSION NUMBER: 1999113838 MEDLINE
DOCUMENT NUMBER: 99113838 PubMed ID: 9916800
TITLE: Synergy of demethylation and ***histone*** ***deacetylase*** ***inhibition*** in the re-expression of genes silenced in ***cancer*** .
AUTHOR: Cameron E E; Bachman K E; Myohanen S; Herman J G; Baylin S B
CORPORATE SOURCE: The Oncology Center, Predoctoral Training Program in Human Genetics, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21231, USA.
SOURCE: NATURE GENETICS, (1999 Jan) 21 (1) 103-7.
Journal code: BRO; 9216904. ISSN: 1061-4036.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990223
Last Updated on STN: 19990223
Entered Medline: 19990210

AB Densely methylated DNA associates with transcriptionally repressive chromatin characterized by the presence of underacetylated histones. Recently, these two epigenetic processes have been dynamically linked. The methyl-CpG-binding protein MeCP2 appears to reside in a complex with ***histone*** ***deacetylase*** activity. MeCP2 can mediate formation of transcriptionally repressive chromatin on methylated promoter templates in vitro, and this process can be reversed by ***trichostatin*** A (TSA), a specific ***inhibitor*** of ***histone*** ***deacetylase*** . Little is known, however, about the relative roles of methylation and ***histone*** ***deacetylase*** activity in the stable ***inhibition*** of transcription on densely methylated endogenous promoters, such as those for silenced alleles of imprinted genes, genes on the female inactive X chromosome and tumour-suppressor genes inactivated in ***cancer*** cells. We show here that the hypermethylated genes MLH1, TIMP3 (TIMP3), CDKN2B (INK4B, p15) and CDKN2A (INK4, p16) cannot be transcriptionally reactivated with TSA alone in tumour cells in which we have shown that TSA alone can upregulate the expression of non-methylated genes. Following minimal demethylation and slight gene reactivation in the presence of low dose 5-aza-2'deoxycytidine (5Aza-dC), however, TSA treatment results in robust re-expression of each gene. TSA does not contribute to demethylation of the genes, and none of the treatments alter the chromatin structure associated with the hypermethylated promoters. Thus, although ***DNA*** ***methylation*** and histone deacetylation appear to act as synergistic layers for the silencing of genes in ***cancer*** , dense CpG island methylation is dominant for the stable maintenance of a silent state at these loci.

L14 ANSWER 24 OF 49 MEDLINE
ACCESSION NUMBER: 91344704 MEDLINE
DOCUMENT NUMBER: 91344704 PubMed ID: 1877400
TITLE: Studies on the mechanisms of ***inhibition*** of L1210 cell growth by 3,4-dihydroxybenzohydroxamic acid and 3,4-dihydroxybenzamidoxime.
AUTHOR: Tihan T; Elford H L; Cory J G
CORPORATE SOURCE: Department of Internal Medicine, University of South Florida College of Medicine, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL 33612.
CONTRACT NUMBER: CA27398 (NCI)
SOURCE: ADVANCES IN ENZYME REGULATION, (1991) 31 71-83.
Journal code: 2LG; 0044263. ISSN: 0065-2571.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199109
ENTRY DATE: Entered STN: 19911013
Last Updated on STN: 19970203
Entered Medline: 19910924

AB Didox and Amidox ***inhibit*** L1210 cell growth in culture. At least one of the mechanisms in the mode(s) of action of the compounds is directed at the ribonucleotide reductase site. Partially purified

preparations of ribonucleotide reductase activity are ***inhibited*** by Amidox and Didox. The formation of deoxycytidine nucleotides from [14C] ***cytidine*** in intact L1210 cells is also blocked. Didox and Amidox cause the decrease in the intracellular pools of the four dNTPs. Hydroxyurea-resistant L1210 cells are not cross-resistant to either Didox or Amidox. These data suggest that Didox and Amidox are not ***inhibiting*** ribonucleotide reductase through a mechanism similar to hydroxyurea.

L14 ANSWER 25 OF 49 MEDLINE
ACCESSION NUMBER: 89328990 MEDLINE
DOCUMENT NUMBER: 89328990 PubMed ID: 2666666
TITLE: Synthesis of acyclonucleoside ***hydroxamic*** ***acids*** as ***inhibitors*** of ribonucleotide reductase.
AUTHOR: Farr R A; Bey P; Sunkara P S; Lippert B J
CORPORATE SOURCE: Merrell Dow Research Institute, Cincinnati, Ohio 45215.
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (1989 Aug) 32 (8) 1879-85.
Journal code: J0F; 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198909
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19970203
Entered Medline: 19890907

AB N-Hydroxy-alpha-(2-hydroxyethoxy)-1(2H)-pyrimidineacetamides 1-3 were synthesized as potential antitumor agents whose mechanism of action would involve ***inhibition*** of ribonucleoside diphosphate reductase (RDPR, EC 1.17.4.1). Acyclonucleoside esters 6-8 were prepared by the stannic chloride catalyzed reaction of methyl chloro[2-(phenylmethoxy)ethoxy]acetate (5) with various silylated pyrimidines, generated in situ from the bases and bis(trimethylsilyl)acetamide. Catalytic didebenzylation of hydroxamate 11 gave 1, while 2 and 3 were synthesized by the reaction of lactones 14 and 22, respectively, with hydroxylamine. In vitro acyclonucleoside ***hydroxamic*** ***acids*** 1-3 were 3-10-fold less potent than hydroxyurea against calf thymus ***cytidine*** diphosphate reductase. 5-Fluorouracil derivative 2 is nearly equipotent with hydroxyurea in ***inhibiting*** the growth of HeLa cells, while 1 is a much weaker ***inhibitor*** and ***cytidine*** derivative 3 is devoid of activity at 200 micrograms/mL.

L14 ANSWER 26 OF 49 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:743205 CAPLUS
DOCUMENT NUMBER: 136:35591
TITLE: Synergistic activation of functional estrogen receptor (ER)-.alpha. by DNA methyltransferase and ***histone*** ***deacetylase*** ***inhibition*** in human ER-.alpha.-negative breast ***cancer*** cells
AUTHOR(S): Yang, Xiaowei; Phillips, Dawn L.; Ferguson, Anne T.; Nelson, William G.; Herman, James G.; Davidson, Nancy E.
CORPORATE SOURCE: The Johns Hopkins Oncology Center, Johns Hopkins University, Baltimore, MD, 21231, USA
SOURCE: Cancer Research (2001), 61(19), 7025-7029
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Formation of transcriptional repression complexes such as DNA methyltransferase (DNMT) 1/ ***histone*** ***deacetylase*** (HDAC) or methyl-CpG binding protein/HDAC is emerging as an important mechanism in silencing a variety of methylated tissue-specific and imprinted genes. Our previous studies showed that treatment of estrogen receptor (ER)-.alpha.-neg. human breast ***cancer*** cells with the DNMT ***inhibitor*** 5-aza-2'-deoxycytidine (5-aza-dC) led to ER mRNA and protein re-expression. Also, the HDAC ***inhibitor*** ***trichostatin*** A (TSA) could induce ER transcript about 5-fold. Here we show that 5-aza-dC alone induced ER transcript about 30-40-fold, and the addn. of TSA elevated ER mRNA expression about 10-fold more in the

human ER-neg. breast ***cancer*** cell lines MDA-MB-231 and MDA-MB-435. Overall, the combination of 5-aza-dC and TSA induced a 300-400-fold increase in ER transcript. Restoration of estrogen responsiveness was demonstrated by the ability of the induced ER protein to elicit estrogen response element-regulated reporter activity from an exogenous plasmid as well as induce expression of the ER target gene, progesterone receptor. The synergistic activation of ER occurs concomitantly with markedly reduced sol. DNMT1 expression and activity, partial demethylation of the ER CpG island, and increased acetylation of histones H3 and H4. These data suggest that the activities of both DNMT1 and HDAC are key regulators of methylation-mediated ER gene silencing.
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 27 OF 49 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:496758 CAPLUS
DOCUMENT NUMBER: 133:205810
TITLE: DNMT1 forms a complex with Rb, E2F1 and HDAC1 and represses transcription from E2F-responsive promoters
AUTHOR(S): Robertson, Keith D.; Ait-Si-Ali, Slimane; Yokochi, Tomoki; Wade, Paul A.; Jones, Peter L.; Wolffe, Alan P.
CORPORATE SOURCE: Laboratory of Molecular Embryology, NICHD, NIH, Bethesda, MD, USA
SOURCE: Nature Genetics (2000), 25(3), 338-342
CODEN: NGENEC; ISSN: 1061-4036
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Methylation of CpG islands is assocd. with transcriptional silencing and the formation of nuclease-resistant chromatin structures enriched in hypoacetylated histones. Methyl-CpG-binding proteins, such as MeCP2, provide a link between methylated DNA and hypoacetylated histones by recruiting histone deacetylase, but the mechanisms establishing the methylation patterns themselves are unknown. Whether DNA methylation is always causal for the assembly of repressive chromatin or whether features of transcriptionally silent chromatin might target methyltransferase remains unresolved. Mammalian DNA methyltransferases show little sequence specificity in vitro, yet methylation can be targeted in vivo within chromosomes to repetitive elements, centromeres and imprinted loci. This targeting is frequently disrupted in tumor cells, resulting in the improper silencing of tumor-suppressor genes assocd. with CpG islands. Here, we show that the predominant mammalian DNA methyltransferase, DNMT1, co-purifies with the retinoblastoma (Rb) tumor suppressor gene product, E2F1, and HDAC1 and that DNMT1 cooperates with Rb to repress transcription from promoters contg. E2F-binding sites. These results establish a link between DNA methylation, histone deacetylase and sequence-specific DNA binding activity, as well as a growth-regulatory pathway that is disrupted in nearly all ***cancer*** cells.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 28 OF 49 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:283153 CAPLUS
DOCUMENT NUMBER: 133:171663
TITLE: Targeting gene regulators for ***cancer*** therapy: Antisense ***inhibitors*** provide new sites for intervention
AUTHOR(S): Besterman, Jeffrey M.; Macleod, A. Robert
CORPORATE SOURCE: Research and development for MethylGene, Inc., Can.
SOURCE: Modern Drug Discovery (2000), 3(3), 51-52, 55-56, 58
CODEN: MDDIFT; ISSN: 1099-8209
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 10 refs. focusing on DNA methyltransferase and histone deacetylases as potential targets for the antitumor antisense therapy.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 29 OF 49 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:484934 CAPLUS

DOCUMENT NUMBER: 129:117832
TITLE: Compositions and methods for restoring a normal pattern of genetic imprinting to cells, diagnostic and therapeutic use, and use in identification of pharmacological compounds
INVENTOR(S): Feinberg, Andrew P.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9829108	A2	19980709	WO 1997-US23991	19971229
WO 9829108	A3	19990218		
W: AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE, DK, DK, EE, EE, ES, FI, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9857223	A1	19980731	AU 1998-57223	19971229
EP 969822	A2	20000112	EP 1997-953486	19971229
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001507703	T2	20010612	JP 1998-530254	19971229
US 6235474	B1	20010522	US 1998-114825	19980714

PRIORITY APPLN. INFO.: US 1996-34095P P 19961230
US 1997-995150 B2 19971229
WO 1997-US23991 W 19971229

AB Compns. and methods for the diagnosis and treatment of diseases, e.g. ***cancer*** , that are assocd. with genetic imprinting are provided. Such compns. and methods are useful in restoring a normal pattern of imprinting to cells. The compns. comprise pharmacol. agents that are involved in imprinting and can be used in preventive and therapeutic methods to restore a normal pattern of imprinting. Such agents are capable of restoring a normal pattern of imprinting to cells. Further methods of the invention include means for identifying pharmacol. compds. that exert their effect by restoring normal imprinting to abnormally imprinted chromosomes and genes. Addnl., the invention could also be used to identify new compds. that exert their effect by restoration of normal imprinting to diseased tissues that exhibit underlying abnormal imprinting.

L14 ANSWER 30 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:261622 BIOSIS
DOCUMENT NUMBER: PREV200200261622
TITLE: Preclinical evaluation of the efficacy of STI571 in combination with a variety of novel anticancer agents.
AUTHOR(S): La Rosee, Paul (1); Johnson, Kara (1); Moseson, Erika M. (1); O'Dwyer, Michael (1); Druker, Brian J. (1)
CORPORATE SOURCE: (1) Division Hematology and Medical Oncology, Oregon Health and Science University, Portland, OR USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 839a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

AB STI571, a Bcr-Abl tyrosine kinase ***inhibitor*** has significant clinical activity in all phases of CML. Although durable responses have been seen in chronic phase patients, not all chronic phase patients achieve a cytogenetic response. Further, resistance or relapse during treatment with single agent STI571 have been observed in the majority of

blast crisis patients. To determine whether the activity of STI571 could be enhanced, combinations of STI571 with other anti-leukemic agents were evaluated for activity against Bcr-Abl positive cell lines and in colony forming assays in vitro. We evaluated the cytotoxicity of arsenic trioxide (As2O3, Trisenox) and the chromatin modifiers 5-Aza-2-deoxycytidine (***decitabine***) and ***Trichostatin*** -A alone and in combination with STI571 against Bcr-Abl positive and negative cell lines and primary CML cells derived from chronic phase patients prior to treatment with STI571. As with other chemotherapeutic agents, significantly higher concentrations of As2O3 were required to achieve a 50% growth ***inhibition*** (IC50) of Bcr-Abl positive cell lines, K562 (1.11 muM+-0.075) and MO7p210 (1.99 muM+-0.22) than those required to ***inhibit*** the growth of Bcr-Abl negative cells, MO7e (0.81 muM+-0.18) and 32D (0.52 muM+-0.18). These levels of As2O3 are within a clinically achievable range. Cotreatment of K562 and MO7p210 cells with approximately equipotent doses of As2O3 and STI571 additively ***inhibits*** proliferation in a growth ***inhibition*** range up to 80%. Data analysis by the median-effect method (Chou & Talalay), which calculates the combination-index (CI) at different levels of ***inhibition*** , suggests that at >80% levels of ***inhibition*** , moderate synergy might be achievable. In colony forming assays using CML patient samples, combination treatment showed increased antiproliferative effects as compared with STI571 alone. Combinations of 0.1 or 0.25 muM STI571 with 0.4 or 0.8muM As2O3 (CFU-GM) and 0.8muM As2O3 (BFU-E) were significantly more potent in ***inhibiting*** colony formation as compared to treatment with STI571 alone. ***Decitabine*** is a hypomethylating agent that has activity in the treatment of CML blast crisis but has a narrow therapeutic window due to hematological toxicity. In MTT-assays with K562 cells, the combination of ***decitabine*** with STI571 revealed synergistic activity as seen by CI-values <1 at the IC50 (CI=0.6+-0.24) and IC75 (CI=0.6+-0.08) doses. This synergistic potential was also seen in MO7p210 cells (IC50: CI=0.81+-0.07 and IC75: CI=0.69+-0.1). Colony forming assays assessing the effects of ***decitabine*** on primary CML cells are ongoing. The triple combination of ***Trichostatin*** -A, a ***histone*** ***deacetylase*** ***inhibitor*** , ***decitabine*** and STI571 indicate antagonism (CI>1), which is in contrast to findings in non-leukemic ***malignant*** cell lines, where the combination of ***Trichostatin*** -A and ***decitabine*** led to enhanced apoptosis compared to single agent treatment. Experiments are ongoing with combination of ***Trichostatin*** -A and STI571 and ***Trichostatin*** -A with ***decitabine*** to determine which of these combinations accounts for this antagonism. These data suggest that combinations of STI571 with As2O3 or ***decitabine*** might be considered as therapeutic alternatives that could circumvent resistance to STI571, particularly in patients with advanced disease.

L14 ANSWER 31 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2002:241192 BIOSIS

DOCUMENT NUMBER: PREV200200241192

TITLE: Transcription modulation: A pilot study of sodium phenylbutyrate plus 5-azacytidine.

AUTHOR(S): Camacho, L. H. (1); Ryan, J.; Chanel, S. (1); Maslak, P. (1); Salomoni, P.; Jakubowski, A. (1); Klimek, V. (1); Camastra, D. (1); Nimer, S. (1); Pandolfi, P. P.; Soignet, S. L. (1)

CORPORATE SOURCE: (1) Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY USA

SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 460a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.

DOCUMENT TYPE: Conference

LANGUAGE: English

AB Transcriptional silencing of tumor suppressor genes occurs in ***cancer*** cell by ***DNA*** ***methylation*** and by histone deacetylation (HDAC). Recently, novel agents that target these mechanisms have been developed. To evaluate the role of transcription modulation as a form of anticancer therapy, we initiated a clinical study with 5-azacytidine (5-AC) plus sodium phenylbutyrate (PB), ***inhibitors***

of methyltransferase and ***histone*** ***deacetylase*** , respectively. Treatment schedule entailed subcutaneous injection of 5-AC for 7 consecutive days (75 mg/m2/day) followed by 5 days of intravenous doses of PB (200 mg/kg/day), repeated on a 21 to 28 day schedule contingent on tolerability and response. To date, 6 pts with myelodysplasia/secondary AML have received at least one cycle of therapy (range, 1-3). Reduction in bone marrow blast count as well as increased percent of myeloid maturation was observed in 4 pts; one pt with relapsed ***leukemia*** post BMT that had a complete elimination of bone marrow blasts after one cycle of therapy, and subsequently underwent a second alloBMT. Peripheral blood samples and bone marrow were collected before 5-AC, on day 8 (at completion of 5-AC, and before beginning PB), and at the completion of PB, and an increase in histone acetylation was consistently detected in peripheral blood and bone marrow samples post PB. Selected genes commonly silenced (eg. p15INK4b in myelogenous ***leukemia***) are being analyzed for alteration in methylation and expression, and alterations in methylation of the p15INK4b (CDKN2b) promoter, a region commonly hypermethylated and associated with transcriptional silencing, is being assessed using real time PCR. Treatment has been relatively well tolerated; adverse reactions associated with 5-AC include fatigue, nausea, vomiting, and local tenderness at injection sites. PB was associated with transient somnolence and drowsiness. This ongoing study will evaluate the effects of these agents upon gene methylation and histone deacetylation in target genes, and the safety and potential antitumor effects of this combination.

L14 ANSWER 32 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:129878 BIOSIS
DOCUMENT NUMBER: PREV200200129878
TITLE: Reactivation of a silenced, methylated p16INK4a gene by low-dose 5-aza-2'-deoxycytidine requires activation of the p38 map kinase signal transduction pathway.
AUTHOR(S): Lavelle, Donald (1); DeSimone, Joseph; Hankewych, Maria; Kousnetzova, Tatiana; Chen, Yi-Hsiang
CORPORATE SOURCE: (1) Department of Medicine, University of Illinois at Chicago, Chicago, IL USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 105a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB ***DNA*** ***methylation*** silences the expression of multiple tumor supressor genes in many types of tumors by inducing repressive chromatin structures mediated by binding of methylated DNA binding (MBD) proteins associated with protein complexes containing ***histone*** ***deacetylase*** (HDAC) activity and chromatin remodeling factors. Treatment with the DNA demethylating drug 5-aza-2'-deoxycytidine (***decitabine*** ; DAC) reactivates the expression of silenced, methylated tumor suppressor genes by alleviating methylation-mediated repression. The synergistic reactivation of silenced, methylated genes by a combination of the HDAC ***inhibitor*** ***trichostatin*** A with low doses of DAC inducing limited demethylation demonstrated the important role of HDAC in the maintenance of methylation-mediated gene silencing (Cameron et al, Nat Genet 21:103, 1999). Whether DAC induces other activities that may be essential in the reactivation of silenced, methylated genes has not been investigated. Environmental and pharmacologic stress activates alternative map kinase signal tranduction pathways resulting in MSK 1-mediated phosphorylation of a minute fraction of histone H3 on serine 10. Phosphorylation of H3 increases sensitivity to hyperacetylation by HDAC ***inhibitors*** and histone acetyltransferases. Our objective in these experiments was to: 1) determine whether DAC treatment activated map kinase signal transduction pathways, and 2) investigate the role of map kinase pathways in the reactivation of silenced, methylated tumor suppressor genes. We observed that DAC treatment reactivated expression of a silenced, methylated p16INK4a gene in HS-Sultan cells in a dose-dependent manner (10-7 to 10-6 M). Phosphorylation of p38 map kinase was increased in a linear, dose-dependent manner at DAC concentrations ranging from 10-8 to 10-6 M. No activation of ERK 1/2 was observed. Increased phosphorylation of p38

was observed as early as 12 hours following drug addition. The ability of DAC to reactivate p16INK4a expression was ***inhibited*** the p38 map kinase ***inhibitor*** SB203580 (10muM) at low doses (10-7 M) but not high doses (10-6 M) of DAC. The degree of ***inhibition*** was reduced with increasing DAC dose. The ERK 1/2 ***inhibitor*** PD098059 had no effect. Neither SB203580 or PD098059 affected cell growth and therefore the ***inhibition*** of p16INK4a reactivation was not due to ***inhibition*** of DAC incorporation into DNA H89 (10muM), at a concentration shown to preferentially ***inhibit*** MSK 1 (Thomson et al, EMBO J:4779, 1999), also ***inhibited*** reactivation of p16INK4a at low doses of DAC, suggesting that MSK 1-mediated histone H3 phosphorylation was required for p16INK4a reactivation. Our results demonstrate that activation of the p38 map kinase signal transduction pathway is required for reactivation of a silenced methylated p16INK4 gene by low dose DAC and suggest that this is due to the induction of an active chromatin configuration through phosphorylation of histone H3 by MSK 1. Therefore, reactivation of a silenced, methylated p16INK4a tumor suppressor gene at low doses of DAC requires both a reduction of ***DNA*** ***methylation*** density leading to loss of repressive MBDHDAC complexes and induction of an active chromatin configuration through the p38 map kinase signal transduction pathway.

L14 ANSWER 33 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:129870 BIOSIS
DOCUMENT NUMBER: PREV200200129870
TITLE: Depsipeptide (FR901228) induces lysine-specific histone acetylation, differentiation and apoptosis in acute myeloid ***leukemia*** cells and demonstrates synergy with ***decitabine*** .
AUTHOR(S): Maghraby, Eman A. (1); Murphy, Thimoty (1); Parthun, Mark R.; Klisovic, Marko (1); Sklenar, Amy; Archer, Kellie J. (1); Whitman, Susan (1); Grever, Michael R. (1); Caligiuri, Michael A. (1); Byrd, John C. (1); Marcucci, Guido (1)
CORPORATE SOURCE: (1) Comprehensive Cancer Center, Ohio State University, Columbus, OH USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 103a-104a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Alterations in histone acetylation and, in turn, chromatin remodeling are important mechanisms in leukemogenesis. In t(8;21)(q22;q22) AML, the AML1/ETO fusion protein disrupts normal hematopoiesis by recruiting the transcription repressor ***histone*** ***deacetylase*** (HDAC) complex NCOR/Sin3/HDAC1 to AML1 target genes. The importance of histone acetylation to other types of AML is uncertain. We Studied the biological effects of depsipeptide (FR901228), a HDAC ***inhibitor*** currently in clinical trials, on both AML1/ETO-positive and negative AML cell lines and primary ***leukemia*** cells. Following 24-hour exposure of AML1/ETO-positive Kasumi-1 cell line to 0.1 to 100 nmol/L depsipeptide, increasing histone H3 and H4 acetylation levels were noted by immunoblotting analysis. These changes occurred in a specific pattern of lysine residue acetylation (i.e., more pronounced at H4 K5, 8 and 12 and less at K16). A significant depsipeptide-induced dose-dependent (0.1 to 100 nmol/L; $p<0.0001$) and time-dependent (4 to 96 h; $p<0.0001$) decrease in cell viability was found as assessed by trypan blue and annexin-V/PI staining. Similar findings relative to loss of viability and change in histone acetylation were observed in the K562 cell line and in primary ***leukemia*** cells. As ***histone*** ***deacetylase*** ***inhibitors*** have been shown to promote differentiation and enhance transcription, we examined for both processes concurrent with in vitro treatment in the Kasumi-1 cell line. Up-regulation of CD11b, a myeloid differentiation antigen, and expression of IL-3, an AML1 target gene, following exposure to depsipetide was demonstrated by flow-cytometry and RT-PCR assays, respectively. We next examined if agents that reverse methylation (ie. ***decitabine***) also increase histone acetylation and apoptosis in AML cells. These studies demonstrated that ***decitabine*** (2.5 umol/L) could enhance histone H4 acetylation at low levels of depsipeptide (1 nmol/L) treatment as compared to

depsipeptide or ***decitabine*** alone. Enhanced acetylation of H4 was associated with a significant higher 24-h apoptosis rate as compared to either agent alone. These data demonstrate that depsipeptide has significant antitumor activity in AML1/ETO-positive cells, and appears to promote transcriptional activation, differentiation, and apoptosis concurrent with increase in H3 and H4 histone acetylation. Furthermore, enhanced acetylation induced by ***decitabine*** markedly increases apoptosis. These results provide a rationale for trials with both single agent depsipeptide and those combining despipeptide with ***decitabine*** for AML treatment that target the pharmacodyamic endpoint of increasing histone acetylation in blast cells.

L14 ANSWER 34 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:1674 BIOSIS
DOCUMENT NUMBER: PREV200200001674
TITLE: Increased expression of MLH1 and sensitization to cisplatin by ***inhibition*** of ***DNA*** ***methylation*** and histone deacetylzation in a small-cell lung ***cancer*** cell line.
AUTHOR(S): Plumb, Jane Anne (1); Strathdee, Gordon; Milroy, Robert; Brown, Robert
CORPORATE SOURCE: (1) CRC Department of Medical Oncology, University of Glasgow, Glasgow UK
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2001) Vol. 42, pp. 813. print.
Meeting Info.: 92nd Annual Meeting of the American Association for Cancer Research New Orleans, LA, USA March 24-28, 2001
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L14 ANSWER 35 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:305376 BIOSIS
DOCUMENT NUMBER: PREV200100305376
TITLE: A phase IIb trial of all-trans retinoic acid (ATRA) combined with bryostatin 1 (BRYO) in patients (pts) with myelodysplastic syndromes (MDS) and acute myeloid ***leukemia*** (AML.
AUTHOR(S): Stone, Richard (1); DeAngelo, Daniel (1); Galinsky, Ilene (1); Yang, Xinping (1); Daftary, Farah (1); Xu, Guangin (1); Liou, Simon (1)
CORPORATE SOURCE: (1) Dana-Farber Cancer Institute, Boston, MA USA
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 2, pp. 265b. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB ATRA, a vitamin A derivative, and BRYO, a macrocyclic lactone isolated from the marine organism B. neritina, synergistically induce monocytic differentiation in human AML cell lines via up-regulation and activation of protein kinase Cbeta (PKCbeta) which initiates cell signaling cascades. A trial in solid tumor pts determined the maximally tolerated dose (MTD) of BRYO that could be given with ATRA at its MTD. We performed a randomized phase IIb trial in which pts with MDS or AML (relapsed/refractory and/or not a chemotherapy candidate) were given ATRA (75 mg/m2 po bid on d1-8, 15-22) in combination with BRYO (60 ug/m2 over 30 min or 40 ug/m2/d for 72 h on d 8 and 22). 40 pts (27M/13F; age 38-80; median 68 years) were enrolled (17 with MDS (RAEB/RAEB-T (9); RA/RARS (8)) and 23 with AML (relapsed/refractory (12); initial treatment (rx) in pts > age 60 years (11))). 38 are evaluable (eval) for toxicity (2 dropped out before BRYO due to sepsis (1) and rapid disease progression (1)) and 36 for response (4 dropped out between d 8-28 due to sepsis, disease progression, or other). While disease-related Gr 3/4 sepsis (9) and GI toxicities (5) were noted, serious study drug-related toxicites were limited to cardiac ischemia (1), severe bone pain (1), and BRYO 30 min infusion-related facial flushing and shortness of breath (4) which did not recur upon rechallenge in 3. Although there were no complete or partial

remissions, 9 (25% of eval pts, 5 in the BRYO 30 min arm) experienced a sustained improvement by at least 50% in at least one parameter. 8 had a reduction in bone marrow blasts and 5 had an improvement in a cytopenia. 8 pts received at least one additional 22 d cycle. The PKCbeta protein level in ficoll-isolated blood mononuclear cells (MNCs), measured by Western blotting of cytoplasmic extracts compared to an actin control, was down-regulated in the cytoplasm (which correlates with enzyme activation) after 15-45 min relative to the start of BRYO rx in 11/11 pts who received BRYO over 30 min and after 1-3d in 7/11 courses in 7 pts who received the 72 h infusion. These results demonstrate that ATRA in combination with BRYO (at both 30 min and 72 h infusion duration) is well tolerated in pts with MDS and AML, has the predicted effect on PKCbeta levels and posesses some clinical activity. Future trials of this combination plus other differentiation inducers, including ***histone*** ***deacetylase*** or ***DNA*** ***methylation*** ***inhibitors*** , may be warranted.

L14 ANSWER 36 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:301438 BIOSIS
DOCUMENT NUMBER: PREV200100301438
TITLE: ***Decitabine*** and sodium butyrate reactivate expression of a silenced Stat-1 and enhance interferon-responsiveness in the HS-Sultan cell line.
AUTHOR(S): Lavelle, Donald (1); Chen, Yi-Hsiang (1); Hankewych, Maria (1); Kourznetsova, Tatiana (1); DeSimone, Joseph (1)
CORPORATE SOURCE: (1) Medicine, Westside Division, VA Chicago, University of Illinois at Chicago, Chicago, IL USA
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 302a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Silencing of Stat-1 gene expression may mediate changes in the growth, survival, and response to interferon of ***cancer*** cells. The level of expression of Stat-1, Stat-2, Stat-3, and Stat-5 in five human ***myeloma*** cell lines (ARH-77, HS-Sultan, OPM-2, RPMI 8226, U266) was measured to assess whether alterations of Stat gene expression are associated with multiple ***myeloma*** . Constitutive expression of these genes was observed by Western blot analysis in all lines except HS-Sultan, in which the expression of Stat-1 was nearly undetectable. Treatment of HS-Sultan cells with the DNA methyltransferase ***inhibitor*** 5-aza-2'-deoxycytidine (***decitabine*** ; DAC) and the ***histone*** ***deacetylase*** ***inhibitors*** , sodium butyrate and ***trichostatin*** A, reactivated Stat-1 mRNA and protein expression as observed by Northern and Western blot analysis. The addition of interferon-alpha resulted in phosphorylation of the Stat-1 protein in HS-Sultan cells pretreated with either ***decitabine*** or sodium butyrate. These results suggest that expression of the Stat-1 gene was silenced by DNA hypermethylation in the HS-Sultan line. The effect of reactivation of Stat-1 expression on the ability of interferon-alpha to ***inhibit*** cell growth was determined by measuring the effect of varying doses of interferon on the growth of untreated control cells compared to cells surviving a 72 hour pretreatment with either butyrate (1mM) or ***decitabine*** (1 X 10-6M). The percent growth ***inhibition*** by interferon-alpha (5000, 1250, 310 U/ml) of control cells was 52.1+-7.0, 43.3+-11.5 and 34.6+-10.9 (n=3), of ***decitabine*** -pretreated cells was 83.2+-6.5, 73.4+-10.1, and 66.0+-17.3 (n=3), and of butyrate-pretreated cells was 79, 65, and 63 (n=1) at the respective doses of interferon. Pretreatment of HS-Sultan with ***decitabine*** or butyrate, which results in reactivation of Stat-1 expression, thus also increases the response to interferon-alpha.

L14 ANSWER 37 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:258571 BIOSIS
DOCUMENT NUMBER: PREV200100258571
TITLE: Induction of HTLV-1 tax and immune genes in infected cells by ***histone*** ***deacetylase*** ***inhibition*** and DNA demethylation agents.

AUTHOR(S): Villanueva, Raul (1); Sanin, Luis; Arturo, Alvaro; Choles, Franklin; Dan[redacted]d, Fernando
CORPORATE SOURCE: (1) Brigham and Women's Hospital, 77 Avenue Louis Pasteur, Him., Boston, MA, 02115 USA
SOURCE: FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A1230. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB HTLV-1 is a retrovirus associated with adult T cell ***leukemia*** / ***lymphoma*** (ATLL) and with the human disease HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP). We sought to determine whether agents that block histone deacetylation or ***DNA*** ***methylation*** could influence the expression of host and viral genes in HTLV-1 infected immune cells. We blocked ***histone*** ***deacetylases*** (HDACs) and ***DNA*** ***methylation*** with ***Trichostatin*** A and 5-Azacytidine, respectively. We found that both treatments led to upregulation of HTLV-1 Tax and of several immune-related mRNAs, including genes with immune suppressor function but also genes involved in tissue infiltration. Our findings have important implications for our understanding of viral and immune gene regulation and for the use of HDAC ***inhibitors*** in the treatment of viral-induced autoimmunity and ***cancer*** .

L14 ANSWER 38 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:182254 BIOSIS
DOCUMENT NUMBER: PREV200100182254
TITLE: New chemotherapy agents in acute ***leukemia*** .
AUTHOR(S): Cheson, Bruce D. (1)
CORPORATE SOURCE: (1) National Cancer Institute and Georgetown University, Washington, DC USA
SOURCE: Annals of Hematology, (2001) Vol. 80, No. Supplement 2, pp. S3. print.
Meeting Info.: Acute Leukemias IX Basic Research, Experimental Approaches and Novel Therapies Munich, Germany February 24-28, 2001
ISSN: 0939-5555.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L14 ANSWER 39 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:69502 BIOSIS
DOCUMENT NUMBER: PREV200100069502
TITLE: Chromatin modification and disease.
AUTHOR(S): Johnson, Colin A. (1)
CORPORATE SOURCE: (1) Chromatin and Gene Expression Group, Department of Anatomy, University of Birmingham, Birmingham, B15 2TT: c.a.johnson@bham.ac.uk UK
SOURCE: Journal of Medical Genetics, (December, 2000) Vol. 37, No. 12, pp. 905-915. print.
ISSN: 0022-2593.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

L14 ANSWER 40 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:261637 BIOSIS
DOCUMENT NUMBER: PREV200000261637
TITLE: Chemotherapy of breast ***cancer*** with ***inhibitors*** of ***DNA*** ***methylation*** 5-aza-2-deoxycytidine and histone deacetylation ***trichostatin*** A.
AUTHOR(S): Bovenzi, Veronica (1); Momparler, R. L.
CORPORATE SOURCE: (1) St Josephine Hosp, Montreal, Quebec Canada
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 603. print..
Meeting Info.: 91st Annual Meeting of the American

Association for Cancer Research. San Francisco, California, USA April 01- 2000
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L14 ANSWER 41 OF 49 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002021366 EMBASE
TITLE: Aberrant methylation and histone deacetylation of cyclooxygenase 2 in gastric ***cancer*** .
AUTHOR: Kikuchi T.; Itoh F.; Toyota M.; Suzuki H.; Yamamoto H.; Fujita M.; Hosokawa M.; Imai K.
CORPORATE SOURCE: F. Itoh, First Dept. of Internal Medicine, Sapporo Medical University, S-1, W-16, Chuo-ku, Sapporo 060-8543, Japan. fitoh@sapmed.ac.jp
SOURCE: International Journal of Cancer, (20 Jan 2002) 97/3 (272-277).
Refs: 35
ISSN: 0020-7136 CODEN: IJCNAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Cyclooxygenase 2 plays a critical role in the development of gastrointestinal ***cancers*** in both human and animal models. About 80% of the gastric ***cancer*** showed a high level of expression of cyclooxygenase 2, but a subset of cases do not express without unknown reason. Aberrant methylation of CpG island of COX-2 was examined by using a series of gastric ***cancer*** cell lines and primary gastric ***cancers*** . Two out of 8 cell lines (25%) and 11 out of 93 (12%) primary ***cancers*** showed aberrant methylation of the 5' region of COX-2. Methylation of COX-2 was closely associated with loss of expression and treatment of methylation ***inhibitor*** , 5-deoxy-2'-azacytidine restored the expression of COX-2. A combined treatment of 5-deoxy-2'-azacytidine and a histone deacetylese ***inhibitor*** , ***trichostatin*** A, restored re-expression of the gene synergistically and chromatin immunoprecipitation analysis revealed that histone of methylated COX-2 promoter is deacetylated, indicating the role of cytosine methylation and histone deacetylation in the silencing of the gene. These results indicate that a subset of gastric ***cancer*** with COX-2 methylation evolves through the pathway that is independent of COX-2 expression and that COX-2 ***inhibitor*** may not be useful to induce apoptosis in these cases. .COPYRGT. 2002 Wiley-Liss, Inc.

L14 ANSWER 42 OF 49 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999294588 EMBASE
TITLE: ***Inhibition*** of ribonucleotide reductase by a new class of isoindole derivatives: Drug synergism with cytarabine (Ara-C) and induction of cellular apoptosis.
AUTHOR: Nandy P.; Lien E.J.; Avramis V.I.
CORPORATE SOURCE: V.I. Avramis, Division of Hematology-Oncology, MS 57, 4650 Sunset Blvd., Los Angeles, CA 90027, United States. vavramis@chla.usc.edu
SOURCE: Anticancer Research, (1999) 19/3 A (1625-1633).
Refs: 42
ISSN: 0250-7005 CODEN: ANTRD4
COUNTRY: Greece
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The hydroxyisoindole dione derivatives ISID and MISID are new compounds with structures resembling purines and possessing a ***hydroxamic*** ***acid*** moiety which is the pharmacophore of hydroxyurea (HU), an ***inhibitor*** of ribonucleotide reductase (RR). ISID and MISID exhibited 100- to 500-fold higher cytotoxicity as compared to HU against

cell lines sensitive (CEM/0) or resistant to ara-C (CEM/ara-C/7A; CEM/dCk[-]). Both MISID and ISID showed significant inhibitory ***activity*** of ribonucleotide reductase (RR). Treatment of CEM/0 cells with 10 .mu.M ISID showed a linear decrease in all the dNTPs leading to a complete depletion by 4 hours with no recovery of enzymatic activity of RR up to 48 hours in the presence of the drug, suggesting an irreversible inhibition ***of*** this enzyme. However, 10 .mu.M MISID caused a significant time dependent, but reversible inhibition ***of*** RR in a whole cell assay in CEM/0 cells. Pretreatment of CEM/0 cells with 10 .mu.M MISID for 1 hour increased cellular ara-CTP concentrations approximately 2-fold as compared to untreated controls. However, a reduction in intracellular ara-CTP concentration was observed following a commensurate depletion of ATP in these cells after 4 hrs of ISID pretreatment. Similarly, the ara-nCTP concentration was augmented by 1.6-fold following pretreatment of CEM/0 cells with 10 .mu.M MISID for 4 hours. Significant apoptotic cell death was detected in CEM/0 cells treated with ara-C, ISID or MISID alone or in combination. Ara-C treatment induced HMW (high molecular weight) DNA fragmentation at earlier times which subsequently led to oligonucleosomal DNA fragmentation by 48 hrs. The sequential treatment of CEM/0 cells with MISID followed by ara-C resulted in increased DNA fragmentation in the 2.0 to 4.0 Kb range in comparison to those cells treated with either ara-C or MISID alone. The increased apoptotic cell death explained the synergistic cytotoxicity of the combination of ara-C and MISID against CEM/0 cells observed earlier. We conclude that the inhibition ***of*** RR by these agents induces leukemic cell apoptosis, a mechanism which is further potentiated when these RR inhibitors ***are*** combined with ara-C. Since new compounds do not require activation, as do other clinically useful RR inhibitors, ***further*** studies for their potential use against leukemias ***and*** solid tumors are warranted.

L14 ANSWER 43 OF 49 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2002:373567 SCISEARCH
THE GENUINE ARTICLE: 546GG
TITLE: Endogenous reactivation of the RAR beta 2 tumor suppressor gene epigenetically silenced in breast ***cancer***
AUTHOR: Sirchia S M; Ren M Q; Pili R; Sironi E; Somenzi G; Ghidoni R; Toma S; Nicolo G; Sacchi N (Reprint)
CORPORATE SOURCE: Johns Hopkins Univ, Sidney Kimmel Comprehens Canc Ctr, BBCRB 406, 1650 Orleans St, Baltimore, MD 21231 USA (Reprint); Johns Hopkins Univ, Sidney Kimmel Comprehens Canc Ctr, Baltimore, MD 21231 USA; Univ Milan, San Paolo Univ Hosp, Sch Med, Lab Genet & Biochem, I-20142 Milan, Italy; Univ Genoa, Dept Oncol Biol & Genet, I-16132 Genoa, Italy; Natl Inst Canc Res, I-16132 Genoa, Italy
COUNTRY OF AUTHOR: USA; Italy
SOURCE: CANCER RESEARCH, (1 MAY 2002) Vol. 62, No. 9, pp. 2455-2461.
Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202 USA.
ISSN: 0008-5472.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 34
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Loss of expression of retinoic acid receptor beta2 (RARbeta2), a potent tumor suppressor gene, is commonly observed during breast carcinogenesis. RARbeta2 silencing can be traced to epigenetic chromatin changes affecting the RARbeta P2 promoter. Here we show that retinoic acid therapy fails to induce RARbeta2 in primary breast tumors, which carry a methylated RARbeta P2 promoter. ***DNA*** ***methylation*** leads to repressive chromatin deacetylation at RARbeta P2. By inducing an appropriate level of histone reacetylation at RARbeta P2 we could reactivate endogenous RARbeta2 transcription from unmethylated as well as methylated RARbeta P2 in breast ***cancer*** cell lines and xenograft tumors, and obtain significant growth ***inhibition*** both in vitro and in vivo. This study may have translational implications for breast ***cancer*** and other ***cancers*** carrying an epigenetically silenced RARbeta P2 promoter.

L14 ANSWER 44 OF 49 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2001:608003 SCISEARCH

THE GENUINE ARTICLE: 456QF
TITLE: Genes, chrom[redacted]n, and breast ***cancer*** [redacted]n epigenetic tale
AUTHOR: Mielnicki L M (Reprint); Asch H L; Asch B B
CORPORATE SOURCE: Roswell Pk Canc Inst, Div Expt Pathol, Elm & Carlton St, Buffalo, NY 14263 USA (Reprint); Roswell Pk Canc Inst, Div Expt Pathol, Buffalo, NY 14263 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF MAMMARY GLAND BIOLOGY AND NEOPLASIA, (APR 2001) Vol. 6, No. 2, pp. 169-182.
Publisher: KLUWER ACADEMIC/PLENUM PUBL, 233 SPRING ST, NEW YORK, NY 10013 USA.
ISSN: 1083-3021.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 129
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The production of heritable changes in gene expression is the driving force in the development and progression of breast ***cancer*** . Such changes can result from mutations or from epigenetic events such as hypermethylation of DNA and hypoacetylation of histones. Histone acetylation and DNA methylation are major determinants of chromatin structure, and chromatin structure is a primary regulator of gene transcription. ***Cancer*** cells frequently contain both mutated genes and genes with altered expression due to one or more epigenetic mechanisms. This review describes the epigenetic changes that disrupt normal chromatin architecture and modify the expression of key genes in breast ***cancer*** cells. The structural integrity of the latter genes is usually intact, but their expression has been substantially altered due to methylation in their promoter region or deacetylation of histones that interact with their promoter region or both mechanisms. Genes affected by epigenetic changes in breast ***cancers*** include BoxA5, p21(WAF), gelsolin, BRCA1, BRCA2, E-cadherin, steroid hormone receptors, and retinoic acid receptor II. Because these epigenetic modifications are usually reversible by treatment with certain drugs, they represent vulnerabilities in the ***cancer*** cell that can be exploited as novel targets for new prevention and therapeutic strategies.

L14 ANSWER 45 OF 49 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2001:557430 SCISEARCH
THE GENUINE ARTICLE: 451YN
TITLE: Hypermethylation leads to silencing of the SYK gene in human breast ***cancer***
AUTHOR: Yuan Y F; Mendez R; Sahin A; Dai J L (Reprint)
CORPORATE SOURCE: Univ Texas, MD Anderson Canc Ctr, Dept Mol Pathol, Box 89, 1515 Holcombe Blvd, Houston, TX 77030 USA (Reprint); Univ Texas, MD Anderson Canc Ctr, Dept Mol Pathol, Houston, TX 77030 USA; Univ Texas, MD Anderson Canc Ctr, Dept Pathol, Houston, TX 77030 USA
COUNTRY OF AUTHOR: USA
SOURCE: CANCER RESEARCH, (15 JUL 2001) Vol. 61, No. 14, pp. 5558-5561.
Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202 USA.
ISSN: 0008-5472.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 32
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A number of ***cancer*** -associated genes have been shown to be inactivated by hypermethylation of CpG islands during breast tumorigenesis. SYK, a candidate tumor suppressor, has been found not expressed in a subset of breast ***cancer*** cell lines, but the mechanism by which SYK is silenced is unclear, In this study, we examined the 5 ' CpG island methylation status of the SYK gene in breast ***cancer*** cell lines and primary breast ***cancer*** tissues. We found SYK 5 ' CpG hypermethylation in 30% (6/20) of breast ***cancer*** cell lines, and the aberrant methylation status was strongly associated with loss of SYK gene expression. Treatment of cells with a methylation ***inhibitor*** , 5-aza-2 ' -deoxycytidine, led to a reactivation of SYK expression in SYK-negative cells, as detected by reverse transcription-PCR, Using methylation-specific PCR, we demonstrated that

SYK is hypermethylated in 32% (12/37) of unselected breast tumors, whereas all of the matched neighboring normal breast tissues exhibited unmethylated DNA status, We concluded that SYK is frequently inactivated through an epigenetic pathway in breast ***cancer*** . Because SYK: has been shown to function as a tumor suppressor, and its loss of expression in breast ***cancer*** has been correlated with tumor invasiveness, the aberrant SYK methylation is responsible for the loss of expression and may consequently play a permissive role for tumor aggressiveness.

L14 ANSWER 46 OF 49 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2001:298593 SCISEARCH
THE GENUINE ARTICLE: 416LG
TITLE: The role of DNA methyltransferase 1 in growth control
AUTHOR: Szyf M (Reprint)
CORPORATE SOURCE: McGill Univ, Dept Pharmacol & Therapeut, 3655 Sir William Osler Promenade, Room 1309, Montreal, PQ H3G 1Y6, Canada (Reprint); McGill Univ, Dept Pharmacol & Therapeut, Montreal, PQ H3G 1Y6, Canada
COUNTRY OF AUTHOR: Canada
SOURCE: FRONTIERS IN BIOSCIENCE, (APR 2001) Vol. 6, pp. D599-D609. Publisher: FRONTIERS IN BIOSCIENCE INC, C/O NORTH SHORE UNIV HOSPITAL, BIOMEDICAL RESEARCH CENTER, 350 COMMUNITY DR, MANHASSET, NY 11030 USA.
ISSN: 1093-9946.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 73
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Vertebrate DNA contains in addition to the four bases comprising the genetic information a modified base, 5-methyl cytosine that plays an important role in the epigenome. The methylated bases form a pattern of methylation that is cell specific and is faithfully inherited during cell division. The enzyme DNA methyltransferase 1 DNMT1 is responsible for copying the DNA methylation pattern but other de novo methyltransferase as well as demethylases might also be involved. Multiple mechanisms are in place to ensure the coordinate inheritance of the DNA methylation pattern with DNA replication. There is a bilateral relationship between the cell cycle and DNMT1. The expression of DNMT1 is tightly regulated with the cell cycle while the expression of DNMT1 can affect the cell cycle. DNMT1 protein might regulate cell cycle events by mechanisms that are independent of its DNA methylation activity through its multiple protein-protein interactions. The unique position of DNMT1 in the cell cycle is consistent with the hypothesis that it plays an important role in ***cancer*** .

L14 ANSWER 47 OF 49 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2000:352025 SCISEARCH
THE GENUINE ARTICLE: 309RL
TITLE: DNA methyltransferase contributes to delayed ischemic brain injury
AUTHOR: Endres M (Reprint); Meisel A; Biniszkiewicz D; Namura S; Prass K; Ruscher K; Lipski A; Jaenisch R; Moskowitz M A; Dirnagl U
CORPORATE SOURCE: HUMBOLDT UNIV, CHARITE HOSP, DEPT NEUROL, DIV EXPT NEUROL, D-10098 BERLIN, GERMANY (Reprint); HARVARD UNIV, MASSACHUSETTS GEN HOSP, SCH MED, STROKE & NEUROVASC REGULAT LAB, BOSTON, MA 02129; MIT, WHITEHEAD INST BIOMED RES, CAMBRIDGE, MA 02142
COUNTRY OF AUTHOR: GERMANY; USA
SOURCE: JOURNAL OF NEUROSCIENCE, (1 MAY 2000) Vol. 20, No. 9, pp. 3175-3181. Publisher: SOC NEUROSCIENCE, 11 DUPONT CIRCLE, NW, STE 500, WASHINGTON, DC 20036.
ISSN: 0270-6474.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 51
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB ***DNA*** ***methylation*** is important for controlling the profile of gene expression and is catalyzed by DNA methyltransferase (MTase), an enzyme that is abundant in brain. Because significant DNA

damage and alterations in gene expression develop as a consequence of cerebral ischemia, we measure MTase activity in vitro and DNA*** ***methylation*** in vivo after mild focal brain ischemia. After 30 min middle cerebral artery occlusion (MCAo) and reperfusion, MTase catalytic activity and the 190 kDa band on immunoblot did not change over time. However, [H-3]methyl-group incorporation into DNA increased significantly in wildtype mice after reperfusion, but not in mutant mice heterozygous for a DNA methyltransferase gene deletion (Dnmt(S/+)). Dnmt(S/+) mice were resistant to mild ischemic damage, suggesting that increased ***DNA*** ***methylation*** is associated with augmented brain injury after MCA occlusion. Consistent with this formulation, treatment with the MTase ***inhibitor*** 5-aza-2'-deoxycytidine and the deacetylation ***inhibitor*** ***trichostatin*** A conferred stroke protection in wild-type mice. In contrast to mild stroke, however, ***DNA*** ***methylation*** was not enhanced, and reduced dnmt gene expression was not protective in an ischemia model of excitotoxic/necrotic cell death. In conclusion, our results demonstrate that MTase activity contributes to poor tissue outcome after mild ischemic brain injury.

L14 ANSWER 48 OF 49 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2000:67234 SCISEARCH
THE GENUINE ARTICLE: 274VA
TITLE: Liver-specific methionine adenosyltransferase MAT1A gene expression is associated with a specific pattern of promoter methylation and histone acetylation: implications for MAT1A silencing during transformation
AUTHOR: Torres L; Avila M A; Carretero M V; Latasa M U; Caballeria J; LopezRodas G; Boukaba A; Lu S C; Franco L; Mato J M (Reprint)
CORPORATE SOURCE: UNIV NAVARRA, FAC MED, DEPT MED INTERNA, DIV HEPATOL & TERAPIA GEN, NAVARRA 31008, SPAIN (Reprint); UNIV NAVARRA, FAC MED, DEPT MED INTERNA, DIV HEPATOL & TERAPIA GEN, NAVARRA 31008, SPAIN; HOSP CLIN BARCELONA, SERV HEPATOL, BARCELONA 08036, SPAIN; UNIV VALENCIA, DEPT BIOQUIM & BIOL MOL, E-46100 VALENCIA, SPAIN; UNIV SO CALIF, SCH MED, DEPT MED, CTR LIVER DIS RES, LOS ANGELES, CA 90033; UNIV SO CALIF, SCH MED, DEPT MED, DIV GASTROINTESTINAL LIVER DIS, LOS ANGELES, CA 90033
COUNTRY OF AUTHOR: SPAIN; USA
SOURCE: FASEB JOURNAL, (JAN 2000) Vol. 14, No. 1, pp. 95-102. Publisher: FEDERATION AMER SOC EXP BIOL, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998. ISSN: 0892-6638.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 35

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Methionine adenoyltransferase (MAT) is the enzyme that catalyses the synthesis of S-adenosylmethionine (AdoMet), the main donor of methyl groups in the cell. In mammals MAT is the product of two genes, MAT1A and MAT2A. MAT1A is expressed only in the mature liver whereas fetal hepatocytes, extrahepatic tissues and liver ***cancer*** cells express MAT2A. The mechanisms behind the tissue and differentiation state specific MAT1A expression are no known. In present work we examined MAT1A promoter methylation status by means of methylation sensitive restriction enzyme analysis. Our data indicate that MAT1A promoter is hypomethylated in liver and hypomethylated in kidney and fetal rat hepatocytes indicating that this modification is tissue specific and developmentally regulated. Immunoprecipitation of mononucleosomes from liver and kidney tissues with antibodies mainly specific to acetylated histone H4 and subsequent Southern blot analysis with MAT1A promoter probe demonstrated that MAT1A expression is linked to elevated levels of chromatin acetylation. Early changes in MAT1A methylation are already observed in the precancerous cirrhotic livers from rats, which slow reduced MAT1A expression. Human hepatoma cell lines which MAT1A is not expressed were also hypermethylated at this locus. Finally we demonstrate that MAT1A expression is reactivated in the human hepatoma cell line hepG2 treated with 5-aza-2'-deoxycytidine or the ***histone*** ***deacetylase*** ***inhibitor*** ***trichostatin*** , suggesting a role for DNA hypermethylation and histone deaceytylation in MAT1A silencing.-Torres, L., Avila, M. A, Carretero, M. V., Latasa, M. U., Caballeria, J., Lopez-Rodas, G., Boukaba,

A., Lu, S. C., Franco, I., Ma[redacted] J.M. Liver-specific methionine adenosyltransferase MAT1A ge[redacted] expression is associated with [redacted] pecific pattern of promoter methylation and histone acetylation; im plications for MAT1A silencing during transformation.

L14 ANSWER 49 OF 49 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 1999:721340 SCISEARCH
THE GENUINE ARTICLE: 236UH
TITLE: Role of histone acetylation and DNA methylation in the maintenance of the imprinted expression of the H19 and Igf2 genes
AUTHOR: Pedone P V; Pikaart M J; Cerrato F; Vernucci M; Ungaro P; Bruni C B; Riccio A (Reprint)
CORPORATE SOURCE: UNIV NAPLES 2, DIPARTIMENTO SCI AMBIENTALI, VIA ARENA 22, I-81100 CASERTA, ITALY (Reprint); UNIV NAPLES 2, DIPARTIMENTO SCI AMBIENTALI, I-81100 CASERTA, ITALY; UNIV NAPLES, CTR ENDOCRINOL & ONCOL SPERIMENTALE, CNR, DIPARTIMENTO BIOL & PATOL CELLULARE & MOL, I-80131 NAPLES, ITALY; NIDDKD, MOL BIOL LAB, NIH, BETHESDA, MD 20892
COUNTRY OF AUTHOR: ITALY; USA
SOURCE: FEBS LETTERS, (10 SEP 1999) Vol. 458, No. 1, pp. 45-50. Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0014-5793.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 40

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB H19 and Ig Igf2 are linked and reciprocally imprinted genes. We demonstrate that the histones associated with the paternally inherited and unexpressed H19 allele are less acetylated than those associated with the maternal expressed allele. Cell growth in the presence of ***inhibitors*** of either ***histone*** ***deacetylase*** or ***DNA*** ***methylation*** activated the silent Igf2 allele, whereas derepression of the silent H19 allele required combined ***inhibition*** of ***DNA*** ***methylation*** and histone deacetylation. Our results indicate that histone acetylation as well as ***DNA*** ***methylation*** contribute to the somatic maintenance of H19 and Igf2 imprinting and that silencing of the imprinted alleles of these two genes is maintained via distinct mechanisms. (C) 1999 Federation of European Biochemical Societies.

=> d his

(FILE 'HOME' ENTERED AT 10:30:45 ON 01 JUN 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 10:31:15 ON 01 JUN 2002

L1	3344	S (DNA METHYLATION) (P) INHIBIT?
L2	31295	S CYTIDINE OR DECITABINE
L3	100	S L1 (P) L2
L4	3881	S (HISTONE DEACETYLASE) (P) INHIBIT?
L5	15569	S (HYDROXAMIC ACID) OR TRICHOSTATIN OR OXAMFLATIN OR (BISHYDROX
L6	1986	S L4 (P) L5
L7	2	S L3 (P) L5
L8	2	DUPLICATE REMOVE L7 (0 DUPLICATES REMOVED)
L9	4175688	S CANCER OR ANTINEOPLASTIC OR CARCINOMA OR SCARCOMA OR SEMINOMA
L10	0	S L7 (P) L9
L11	174434	S DOXORUBCIN OR DAUNORUBICIN OR EPIRUBCIN OR IDARUBICIN OR ANTH
L12	133	S (L1 OR L2) AND (L4 OR L5) AND (L9 OR L11)
L13	50	DUPLICATE REMOVE L12 (83 DUPLICATES REMOVED)
L14	49	S L13 (P) INHIBIT?
L15	2	S L3 AND L6
L16	0	S L15 NOT L7
L17	0	S L7 AND L11
L18	27300	S (DNA METHYLATION) OR (HISTONE DEACEYTLASE)
L19	0	S (DNA METHYLATION) (P) (HISTONE DEACEYTLASE)

=> log y
COST IN U.S. DOLLARS SINCE FILE TOTAL

	ENTRY	SESSION
FULL ESTIMATED COST	182.56	18[redacted]7

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-2.48	-2.48

STN INTERNATIONAL LOGOFF AT 10:54:30 ON 01 JUN 2002